IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BIODELIVERY SCIENCES INTERNATIONAL, INC. and ARIUS TWO, INC.,	)	
Plaintiffs,	)	C.A. No. 18-1395 (CFC) (CJB)
v.	)	
ALVOGEN PB RESEARCH & DEVELOPMENT LLC, ALVOGEN MALTA OPERATIONS LTD., ALVOGEN PINE BROOK LLC, ALVOGEN, INC., and ALVOGEN GROUP, INC.,	)	
Defendants.	)	

PLAINTIFFS' POST-TRIAL BRIEF

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CASES

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TABLE OF ABBREVIATIONS

"the '866 patent"	U.S. Patent No. 8,147,866
"the '843 patent"	U.S. Patent No. 9,655,843
"the '539 patent"	U.S. Patent No. 9,901,539
"BDSI"	BioDelivery Sciences Incorporated
"PTO"	U.S. Patent and Trademark Office
"DEA"	Drug Enforcement Administration
"FDA"	U.S. Food and Drug Administration
"JTX"	Joint Trial Exhibit
"PTX"	Plaintiffs' Trial Exhibit
"DTX"	Defendants' Trial Exhibit
"DBr. __"	Defendants' Opening Post-Trial Brief at a particular page
"DFF ___"	Defendants Finding of Fact
"IPR"	*Inter Partes* Review
"POSA"	Person of Ordinary Skill in the Art
"POSAs"	Persons of Ordinary Skill in the Art
col.xx:yy	For a cite to a patent, "xx" refers to column, "yy" refers to line
Tr.xx:yy	For a cite to a transcript, "xx" refers to particular page of minuscript, "yy" refers to line

Note: all emphasis to the text of this brief is added unless otherwise specified.

I. INTRODUCTION

This case involves BELBUCA®, a novel bioerodible buccal film drug delivery device containing the medicine buprenorphine. BELBUCA is approved by the FDA for the treatment of chronic pain and self-administration by patients. BELBUCA is a two-layered solid film, and the underlying technology is claimed by the '866, '843, and '539 patents-in-suit. The buccal film is placed against and adheres to the inside of a patient's cheek. As the device bioerodes and disappears entirely, the buprenorphine is efficiently absorbed into a patient's blood through the buccal (i.e., cheek) mucosa. BELBUCA's two-layers (front and back) enhance the uptake of buprenorphine through the buccal membrane and into a patient's blood. "Uptake" of a pharmaceutical delivery device is measured by "bioavailability," a term meaning the percentage of drug that reaches and is absorbed into the blood, or maximum plasma concentration of the pharmaceutical in the blood, referred to as C_{max}. Because of the highly efficient delivery system of the underlying invention, BELBUCA is safe and effective with less risk of abuse, death, and debilitating side-effects compared to other marketed opioids.

Defendants have conceded infringement to all nine asserted claims, and the only issue before the Court is whether Defendants have overcome the presumption of validity for these claims by clear and convincing evidence. Defendants have not satisfied this heavy burden.

For anticipation, Defendants must show by clear and convincing evidence that: (1) a single reference is prior art to the patents-in-suit *and* (2) that the single reference discloses the claimed invention exactly as it is arranged and recited in the challenged claims. Defendants cannot satisfy these criteria as no single reference meets these criteria for any of the asserted claims.

For obviousness, Defendants must show by clear and convincing evidence that a POSA would have been: (1) motivated to make the requisite combinations of prior art, *and* (2) would have combined those prior art references with a reasonable expectation of success. Defendants cannot meet this standard. Indeed, Defendants' reliance on a myriad of combinations of at least *nine* different references to patch together the claimed invention strongly negates any possible finding of obviousness. (*See* DBr.16-27.)

Defendants' obviousness defense is primarily based on a misrepresentation of the invention of the patents-in-suit. Defendants create a strawman that misstates the invention, and then attempt to knock down their own strawman. In this regard, Defendants argue that as of the 2006 priority date of the '866 and '843 patents, a POSA would have been able to make a formulation buffered to a pH between about 4 and about 6, such that buprenorphine was "soluble. Solubility is a measure of the amount of medicine that will dissolve in a solvent. Defendants then argue

that a soluble formulation would have been expected to deliver buprenorphine across the buccal mucosa and be "absorbed" into a patient's blood.

But the current invention is not directed to "soluble" buprenorphine that achieves "some" level of absorption, regardless of how inefficient that level of absorption may be. Instead, the claimed invention is directed to the *enhanced uptake* (i.e., absorption) of buprenorphine. The patents are entitled "transmucosal delivery devices with *enhanced uptake*," the abstracts discuss "enhancing transmucosal uptake of . . . buprenorphine," the specification repeatedly discuss "*enhanced delivery*" of buprenorphine, and the asserted claims include elements reciting a "method for providing enhanced uptake of buprenorphine. (*See e.g.*, JTX-0001-0001, 0006-0007, 0018; Tr.584:20-22.) As reflected by the data in evidence, the buccal film delivery devices claimed by the patents-in-suit have significantly enhanced bioavailability versus any of the cited prior art references. (*See* §II.B, *infra*.) Based on the enhanced bioavailability and plasma concentrations achieved by the claimed invention, less buprenorphine is needed, which leads to fewer side effects and "the rapid and efficient delivery of buprenorphine," as recited in the claims. (JTX-001,0019.)

Moreover, the evidence at trial established that a POSA would *not* have been motivated to use *lower* pH values of between about 4 to 6 to enhance the uptake and bioavailability of buprenorphine. All the prior art uniformly taught the exact

opposite—that is, for weakly basic drugs, including buprenorphine, the unionized form of the drugs at *higher* pH values would produce higher bioavailability. (*See* §II.B., *infra*.) Indeed, in 2007, years before formulating her opinions in this case, Defendants' expert Dr. Michniak-Kohn stated with certainty in her own peer-reviewed published scientific work that "studies conducted with sublingual administration of opioids such as buprenorphine, methadone, and fentanyl *showed increased absorption with increase in pH, where the drug was predominantly present in the unionized form.*" (DTX-355-0011.) Consequently, in 2006, a POSA would not have been motivated to use the invention's claimed *lower* pH ranges to enhance the uptake/bioavailability of buprenorphine.

Further, obviousness requires not only a strong showing of motivation but also a reasonable expectation of success. Even if there was motivation to use the lower pH values recited in the patent, which there was not, a POSA would never have reasonably expected the enormous increases in bioavailability achieved by the claimed invention. This enhanced uptake achieved by the claimed lower pH ranges was a total surprise to the inventors themselves since the prior art that addressed pH and the bioavailability of weakly basic drugs like buprenorphine all taught that the exact opposite should have occurred. (*See* §II.B at 15-17, *infra*.) These dramatic and unexpected increases in bioavailability at the claimed pH ranges negate any expectation of success and constitute strong evidence of

unexpected results. In *Orexo AB v. Actavis Elizabeth LLC*, 903 F.3d 1265, 1274 (Fed. Cir. 2018), the Federal Circuit held a patent non-obvious based on a 66% increase in bioavailability over the prior art. The enhanced bioavailability produced by the two-layer bioerodible buccal film device in this case is even higher than that in *Orexo*, with certain devices achieving 200% enhanced uptake of buprenorphine over Suboxone® (a sublingual formulation).

Additionally, the claimed drug delivery devices achieve favorable pharmacokinetic properties that are recited as additional elements in claims 4 and 5 of the '866 patent. Claim 4 requires that "a first quantifiable plasma concentration of buprenorphine is observed at about 45 minutes." (JTX-0001-0019.) Claim 5 requires "an effective plasma concentration of buprenorphine is maintained for at least 4 hours." (*Id.*) Defendants fail to cite any prior art references in which the additional pharmacokinetic properties of claims 4 and 5 of the '866 patent are taught using the method in the patents-in-suit. There is no prior art that taught these pharmacokinetic elements using a bioerodible buccal film. Defendants' reliance on Bullingham-I, a scientifically flawed study in which post-surgical acute-pain patients were given buprenorphine intravenously and then by sublingual tablet, wholly fails to show by clear and convincing evidence that the pharmacokinetic elements of claims 4 and 5 are obvious.

Apparently realizing that they are not able to meet the requisite standard to prove obviousness by clear and convincing evidence with respect to any of the asserted claims, Defendants have attempted to recast their case, albeit *after* trial, by unfairly and improperly raising numerous alleged defenses for the first time in their Post-trial Brief, and even by improperly quoting from a document that was never introduced into evidence at trial. Those previously unasserted arguments should be stricken.

Most noteworthy, Defendants allege that the inventors made "materially false statements" during prosecution with the intent to obtain the patents "under false pretenses." (DBr.51.) Given that Defendants never raised inequitable conduct at *any* stage of this litigation, Defendants rely on case law that predates the current standards of inequitable conduct established by the Federal Circuit in attempt to show that the patents are tainted, and that Defendants' burden of proof is thus lessened. But as such arguments were never raised, they are thus waived. Moreover, there were no false statements, intent to mislead, or showing that but for the allegations made by the Defendants, the PTO would have acted differently—precisely why the defense of inequitable conduct was never pled, raised in any contention, or litigated. Defendants have failed to prove a case of inequitable conduct or to cite to any Federal Circuit precedent supporting its legal argument in

support of reducing its high burden of proof to invalidate the patents based on its asserted obviousness and anticipation defenses.

II. THE DISCOVERY OF THE CLAIMED INVENTION

A. There Was a Need for a Safe and Effective Medicine to Treat Chronic Pain in 2006 that Patients Could Self-Administer

BDSI is a small and growing company in North Carolina that was formed to develop BELBUCA, the lifeblood of BDSI. The development of BELBUCA proceeded for more than 10-years and required a considerable investment of time, effort, and financial resources, particularly for a small company. The inventors began experimentation by 2006, and BELBUCA received FDA approval in 2015 and was first marketed in 2016. (Tr.894:10-14.) Even though it is an opioid, BELBUCA is a safe and effective medicine for the treatment of chronic pain. Chronic pain is "pain that has been present for more than three months, and which may be persistent or intermittent." (DTX-165-0008.) In contrast, "acute pain," is pain that is generally "associated with a particular injury or procedure" such as surgery. (*Id.*)

From 1999 through 2006, deaths due to opioid abuse were increasing dramatically—the number of fatal poisonings involving opioids more than tripled from 4,000 to 13,800 deaths per year. (JTX-410-0001.) Opioids were involved in almost 40% of all poisoning deaths in 2007. (*Id.*) It is undisputed that

practitioners were aware of these deaths as of the "early 2000s." (Tr. 545:17-549:17, 936:14-22, *see also* JTX-399-0002 & 0012 n.9.)

There was a need for a safe medicine that could effectively treat chronic pain and had a lower potential for death and abuse. (Tr.874:14-23.) Buprenorphine was a known chemical compound as of 2006, however, it had a high-first-pass effect, which meant it was essentially not bioavailable when swallowed, and the body could thus not absorb it for therapeutic effect. (DTX-165-0001, 0002.)

Thus, as of 2006, there were only two buprenorphine products marketed in the United States. Buprenex® was an intravenous/injectable formulation. (JTX. 415.) Because it was an injectable formulation, Buprenex® was administered by healthcare providers for moderate to severe acute type pain and was not intended for home injection by patients. (Tr.878:17-879:3.) This made Buprenex® inappropriate for treating chronic pain, which requires patients to be able to self-administer the drug on a daily basis and multiple times a day. (Tr.878:17-879:9.) For this reason, Buprenex had "no clinical utility for chronic pain clinics." (Tr.879:8-9.)

The other FDA-approved buprenorphine product was a sublingual tablet, Suboxone. Sublingual tablets are placed under a patient's tongue and dissolve in saliva while under the tongue over time. Suboxone was (and is still today) only approved by the FDA for the treatment of opioid addiction. (Tr.522:4-13, 875:17-

877:25.) The amount of buprenorphine in Suboxone is very high, the highest dose being some four-times higher than the highest dose of BELBUCA because Suboxone has a low bioavailability of only 25%. (DTX-165-0007, Fig. 3, Tr.521:12-24.) This means that only 25% of the buprenorphine in the tablet is available to the patient for therapeutic effect when used as prescribed. There are no published studies showing that Suboxone can be used to treat chronic pain and scientists have *never* reached a consensus regarding its ability to do so. (JTX 229-0001, 0006; Tr.528:18-531:16, 538:20-539:3, 876:19-877:3.) In sum, in 2006, there were no FDA-approved buprenorphine products for the treatment of chronic pain.

B. The Inventors Developed A Buccal-Film Capable of Enhancing the Uptake of Buprenorphine, Delivering High Plasma Concenrations and Achieving High Bioavailability

The inventors sought to develop formulations for buprenorphine that could be widely used and self-administered by patients for the treatment of chronic pain and that had enhanced bioavailability that would result in much more efficient delivery of the medicine, thus requiring lower doses and reduce unwanted side effects. (JTX-001, col.4:35-42.) Buprenorphine is a weakly basic compound with a pKa (a measure of how basic or acidic a compound is) of around 8.3. (Tr.756:3-5.) For weakly basic compounds, like buprenorphine, the prior art *uniformly* stated that the absorption increases as the pH increases towards the pKa of the compound,

and the compound thus becomes more unionized. (Tr.795:1-800:7, 730:19-731:21, 629:22-630:6, 644:19-647:25.) This scientific principle is referred to as the partition theory. (Tr.795:1-9,796:20-25.)

For example, Stanley-1994 stated that "[i]t has been found in the art that "administration of drugs through the mucosal tissues generally occurs best when the drug is in the *unionized form*," which requires a higher pH. (JTX-250, col.4:49-58; Tr.644:22-645:13.) If the drug exists in "the ionized from [lower pH], which is largely unavailable for transfer across the mucosal tissues." (*Id.*)

Similarly, Weinberg-1988 taught a "pH favoring un-ionization maximized concentration independent drug absorption." (JTX-249-0007; Tr.645:20-646:6.) Weinberg specifically made this statement concerning "[m]ethadone, fentanyl, and buprenorphine." (*Id.*) Defendants' expert, Dr. Michniak-Kohn, citing the same Weinberg reference, wrote in her peer-reviewed 2007 book that "studies conducted with sublingual administration of opioids such as buprenorphine, methadone, and fentanyl showed increased absorption with increase in pH, where the drug was predominantly present in the unionized form." (DTX-355-0011; Tr.251:14-252:2.)

Streisand-1995 also stated that for buccal absorption, "the bioavailability, permeability of fentanyl, are markedly increased as the pH of the fentanyl solution becomes more basic. Most likely, this is because of an increase in the fraction of un-ionized fentanyl." (JTX-0246-0001; Tr.646:7-17.) Fentanyl is a weakly basic

drug like buprenorphine with a similar pKa and was believed to behave similarly. (JTX-249-0006; Tr.755:21-756:7.)

Hague-2004 explained that "adding an ionization agent that maintains a more acidic pH […] which may lead to a decrease in the oral transmucosal absorption and hence bioavailability." (JTX-462, ¶53; Tr.647:1-11.)) Zhang-2001 similarly stated that the "ionized forms almost always have lower partition coefficients than the unionized forms, and therefore are less well absorbed by the oral mucosal tissue." (JTX-243, col.4:58-62; Tr.647:12-25.)

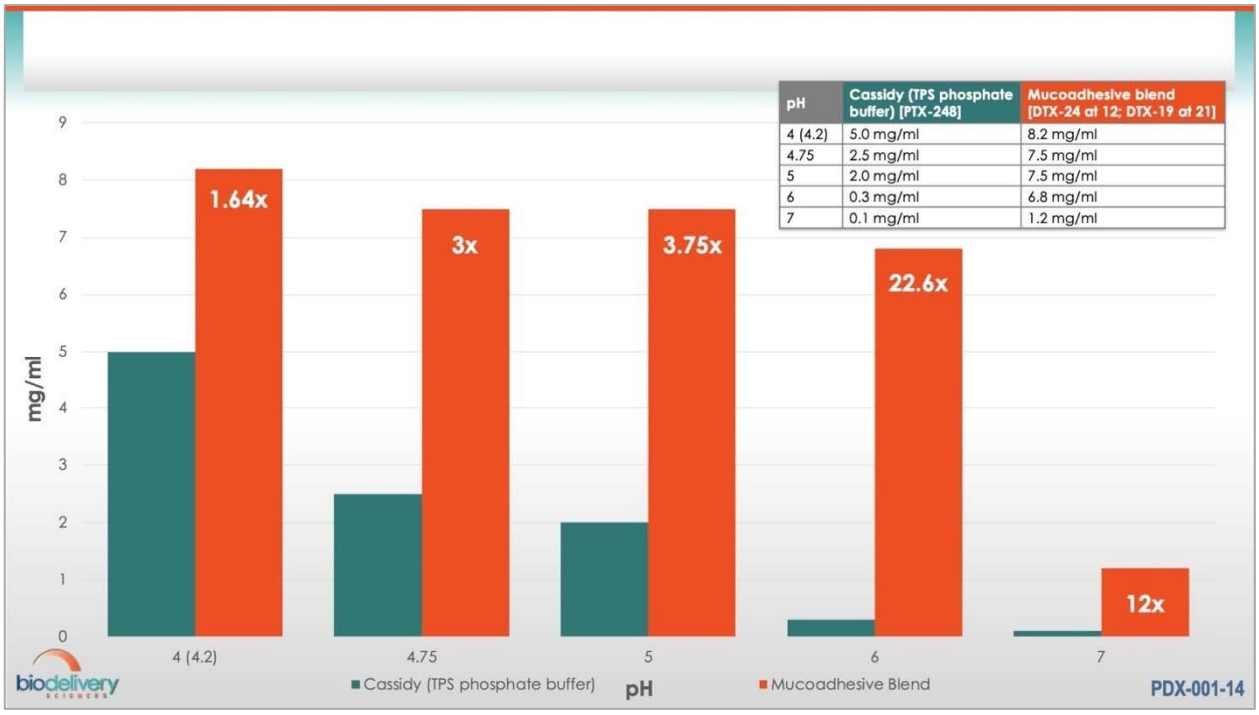
Accordingly, the prior art unambiguously showed that if a POSA wanted better absorption through the mucosa and higher bioavailability, such a person should use a *higher* pH for weakly basic compounds, including buprenorphine, just as Defendants' expert, Dr. Michniak-Kohn, stated in 2007. (Tr.795:1-800:7; DTX-355-0011.) But there was a problem with the existing liquid sublingual formulations that the prior art discussed. As pH was increased to allow for better absorption and bioavailability in the sublingual devices, weakly basic drugs such as fentanyl and buprenorphine became less soluble in liquid solutions, leading to drug stability issues. Weinberg itself stated it wanted to test buprenorphine at even higher pH's but could not do so because of the difficulties in solubilizing buprenorphine in the liquid formulations it was using. (JTX-249-0006.) Thus, the prior art showed that there was a trade-off that had to be made with the liquid-

sublingual formulations—scientists wanted a higher pH to improve bioavailability but were concerned about going to high because of solubility concerns. (JTX-243-col.4:62-63 ("converting the weak acid or base to an ionized form to increase solubility compromises absorption").)

This same concern was also discussed in Cassidy that contained a solubility curve for buprenorphine in different buffered buprenorphine solutions. (JTX-248-0004, Fig. 1.) This curve showed that for the higher pHs, where a POSA would have expected to achieve increased absorption, which are on the right side of the curve, a POSA would have trouble solubilizing high amounts of buprenorphine. (*See e.g.*,Tr.170:20-22;176:1-9.) Thus, if a POSA was using a liquid formulation, or a sublingual tablet formulation like Suboxone, which is designed to dissolve in saliva under the tongue, the POSA was unable to use the more basic pH ranges that were known to work best to enhance uptake, and therefore, such formulations had low bioavailability. (DTX-165-0006-0007, Fig. 3; Tr.516:15-521:24.)

The inventors of the present invention successfully overcame the solubility/low bioavailability problem observed in the prior art. To create a formulation that worked to enhance the bioavailability of buprenorphine, the inventors designed a two-layer bioerodible drug delivery device containing a backing layer and a mucoadhesive layer. The mucoadhesive layer was made up of a particular ratio of polymers created by the inventors, which the inventors referred

to as a "polymeric diffusion environment." (JTX-001-0007,col.4:32-46; JTX-0005-2771.) This polymeric diffusion environment, as demonstrated by the chart below, dramatically increased the solubility of buprenorphine at the higher pH ranges thought by the prior art to be most useful to obtain enhanced bioavailability, which are on the right side of the chart. (Tr.706:4-19.)



(*Compare* DTX-024,p.12(Fig. 3) *with* JTX-248-00412(Fig 1); Tr.620:9-621:19; DTX-071-0021(Fig. 7); DTX-370-0020(Fig. 7).)

For example, at pH 7, the solubility of buprenorphine in the polymeric diffusion environment was some 12 times greater than that shown by Cassidy for simple liquid buffered solutions, and at pH 6, the solubility of buprenorphine was some 22 times more than that shown by Cassidy. (Tr.624:17-23.) The increased

solubility was achieved because the buprenorphine was "molecularly dispersed or dissolved" in the polymers of the mucoadhesive layer creating what is referred to as a "solid solution." (Tr.588:9-20,621:15-622:12.)

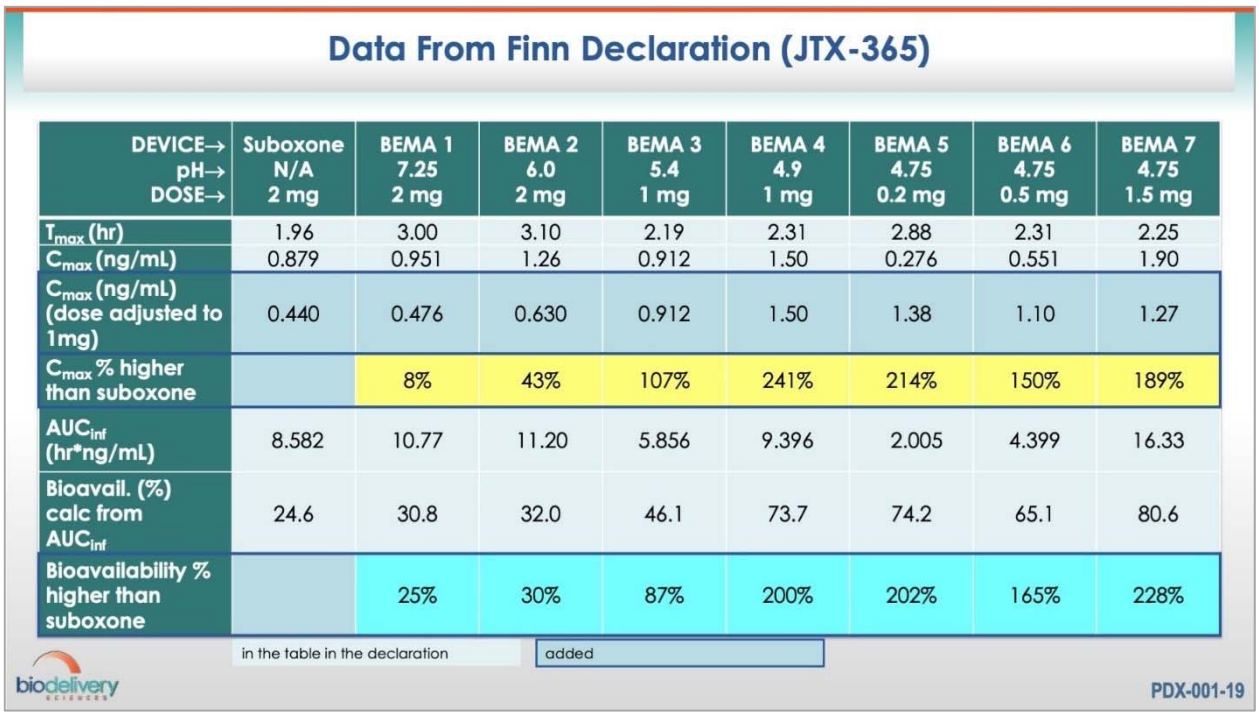
Armed with the knowledge of the increased solubility of buprenorphine in their invention, the inventors designed formulations and tested them in humans using pHs of 6 and 7.25, as those were the pH's taught by the prior art to provide the best bioavailability. Indeed, consistent with the prior art, the inventors had tried using fentanyl in their polymeric diffusion environment, and the device with the pH of 7.25 was shown to have enhanced uptake over the device with a pH of 6.0. (JTX-001,col.23:63-64; Tr.754:24-755:12, 755:19-756:7.) Further, as testified by the inventors, there was no question that the buprenorphine was solubilized in these devices. (Tr.762:21-763:9, 754:5, 755:8-10.)

In addition to the polymeric diffusion environment (which is within the mucoadhesive layer), the two-layer device also had a backing layer three times the thickness of the mucoadhesive layer. (Tr.592:6-17.) The backing layer protects the mucoadhesive layer from saliva as long as possible so that the buprenorphine (which is already solubilized in the polymeric diffusion environment) flows directly into the mucosa—referred to as an "unidirectional gradient"—and *not* into the oral cavity where it can be swallowed and cause unwanted side effects in the

gastrointestinal tract, such as severe constipation. (JTX-001, col.14:24-33; Tr.588:12-20, 592:6-593:25, 770:4-770:23, 873:12-874:13.)

The inventors tested two of their devices, one with a pH of 7.25, the other with a pH of 6.0, in humans in a study identified as "BUP 101". (Tr.757:2-758:4, 771:4-772:14.) The results were promising, as they obtain enhanced C_{max} values that were better than Suboxone® with both the devices at 7.26 and 6.0. (JTX-001, Fig. 3, col.25:55-col.26:10.) The inventors were able to achieve a first measurable plasma concentration (referred to as "T_{first}") at 45 minutes and were able to maintain effective plasma concentrations for at least four hours. (*Id.*)

The inventors also observed something totally unexpected and surprising with respect to bioavailability. The device with a pH of 6.0 had a *higher* bioavailability and C_{max} than the device with a pH of 7.25. This is the *opposite* of the results the inventors themselves had obtained from fentanyl, where the films with the higher pH values had increased bioavailability (Tr.753:17-754:16, 755:1-756:7), and the *opposite* of the teaching of the prior art discussed above. In light of this new and unexpected information, the inventors decided to test even lower pH's and designed devices with pH's of 5.4, 4.9, and 4.75. (Tr.754:14-16). These trials were conducted according to FDA standards in humans. (JTX-365-0003, ¶8.) The results of these low pH tests were nothing short of "tremendous" or "exceptional," as shown below. (Tr.802:21-24.)



Data From Finn Declaration (JTX-365)

DEVICE→ pH→ DOSE→	Suboxone N/A 2 mg	BEMA 1 7.25 2 mg	BEMA 2 6.0 2 mg	BEMA 3 5.4 1 mg	BEMA 4 4.9 1 mg	BEMA 5 4.75 0.2 mg	BEMA 6 4.75 0.5 mg	BEMA 7 4.75 1.5 mg
T_{max} (hr)	1.96	3.00	3.10	2.19	2.31	2.88	2.31	2.25
C_{max} (ng/mL)	0.879	0.951	1.26	0.912	1.50	0.276	0.551	1.90
C_{max} (ng/mL) (dose adjusted to 1mg)	0.440	0.476	0.630	0.912	1.50	1.38	1.10	1.27
C_{max} % higher than suboxone		8%	43%	107%	241%	214%	150%	189%
AUC_{inf} (hr*ng/mL)	8.582	10.77	11.20	5.856	9.396	2.005	4.399	16.33
Bioavail. (%) calc from AUC_{inf}	24.6	30.8	32.0	46.1	73.7	74.2	65.1	80.6
Bioavailability % higher than suboxone		25%	30%	87%	200%	202%	165%	228%

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(JTX-365-0003-04; JTX-352-0007; JTX-353-2009, 1123, 2004; JTX-0349-0042-43.) The results showed a clear and unmistakable trend that the lower the pH, the higher bioavailability, up to as high as 80.6% for a pH of 4.75. This is essentially the same bioavailability obtained from an intramuscular injection (DTX-0165, Fig. 3), which was considered the highest bioavailability formulation—other than intravenous which is administered directly into the blood stream and has 100% bioavailability. (Tr.800:15-801:22.) The results for the bioavailability of BEMA 4, 5, 6, and 7, are some 200%, 202%, 165%, and 228% *higher* than Suboxone®. (Tr.649:1-650:8, 801:3-802:24.)

Dr. Finn, one of the inventors, testified why these results were surprising: "we're moving further and further away from the pKa . . . so there's more ionized

drug at this pH than there is at a pH of 7.25. And the product is soluble -- the buprenorphine is soluble at pH 7.25. So, solubility isn't the issue. It's really something . . . bioavailability is increase[ing], and it's moving away from the pKa, which is surprising, totally surprising." (Tr.771:20-772:6.)

Similarly, Dr. Vasisht, the other inventor, testified that "based on unionized drug concepts that have been there, the higher the pH—if its soluble, the higher the pH, the better the absorption." (Tr.760:2-5, 741:12-21.) Thus, Dr. Vasisht explained that "it is a surprise that the lower pH, more acidic environment works better," and further stated that it was "even more surprising that later studies show that going lower . . . provides a much higher bioavailability." (Tr.760:6-11.)

C. The Claimed Devices Provide a Safe and Effective Medicine to Treat Chronic Pain

Because of the enhanced bioavailability and rapid and efficient delivery, the inventors were able to design formulations for BELBUCA that contained *less* buprenorphine, but still achieved a high degree of efficacy with a low degree of side effects and very little respiratory depression, which is the reason people overdose on opioids. (JTX-001, col.4:35-42, col.11:17-19; JTX-473; JTX-388.) Indeed, there has been no evidence that BELBUCA caused respiratory depression in *any* of the clinical trials. (JTX-404-0007; JTX-433-0010; JTX-405-0007.) "Respiratory depression was not induced following the administration of BELBUCA to over 2400 unique subjects." (Tr.886:2-5; PTX-1060; PTX-1059.)

There were "just two adverse events of respiratory failure and neither of them were considered related to buprenorphine." (Tr.886:6-8.) In this regard, BELBUCA is a Schedule III medicine,[1] which means the DEA has determined that BELBUCA is less prone to abuse than schedule II opioids like Fentanyl and oxycontin. (Tr.539:4-18, 491:12-492:10, 765:15-24.) And as a Schedule III drug, doctors are more easily able to prescribe and refile the prescription without the limitations required with Schedule II drugs. (Tr.766:3-7, 870:23-872:8.)

Further, opioid-induced constipation is a serious debilitating problem for patients, and there is a whole class of medicines that have been developed to treat this serious disorder. (Tr.873:12-874:13.) For BELBUCA, however, the rate of constipation among both opioid-naïve and opioid-experienced patients administered is low and "similar to placebo." (JTX-433-0010; JTX-404-0008; JTX-405-0005.) For other opioids, constipation has been reported as experienced by up to 70% of patients, and an active bowel regimen is typically required to reduce constipation, including the administration of prescription drugs. (Tr.873:12-874:13, 899:7-11.) BELBUCA achieved lower rates of constipation without a bowel regimen. (*See* JTX-404-0008.)

BELBUCA (JTX-233) is unquestionably a safe medicine that provides significant advantages beyond the schedule II opioids then available as of the filing

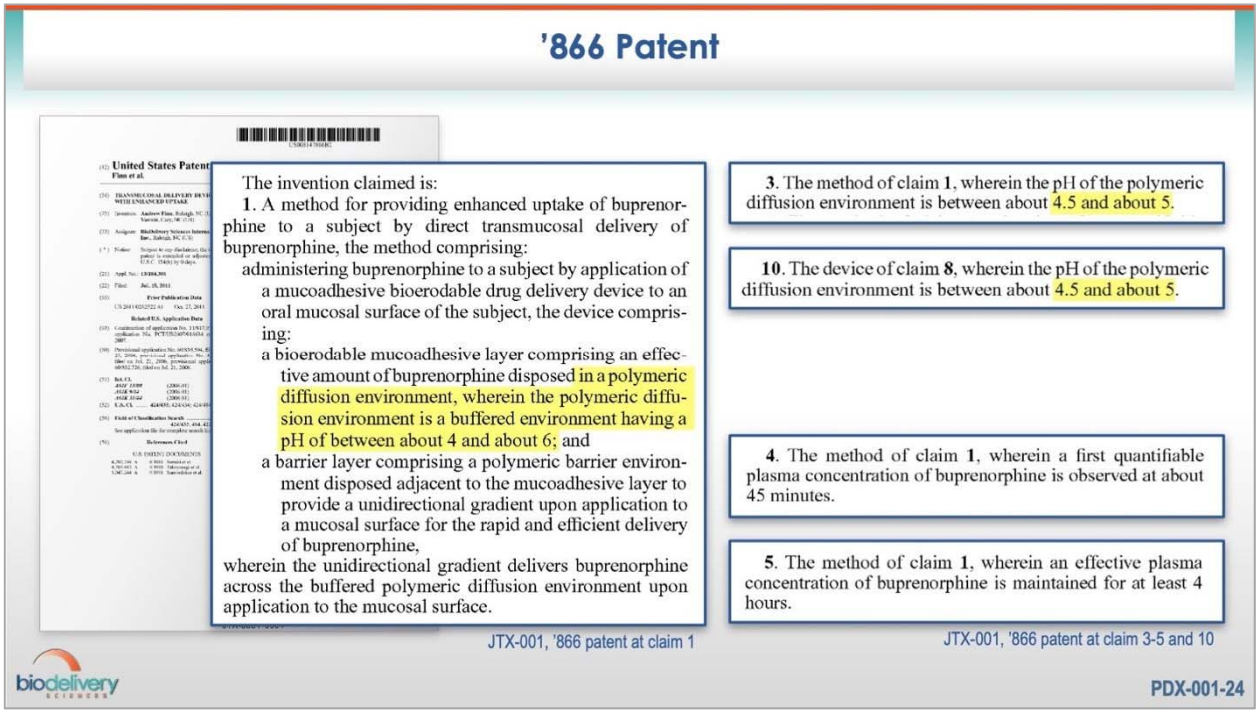
[1] *See* Tr.874:25-875:4 (discussing DEA drug scheduling parameters).

date of the ’866 and ’843 patents. And contrary to Defendants’ assertions, that BELBUCA contains a “class warning” on its label does not mean that the benefits of BELBUCA do not exist. Class warnings are required for all opioids. As specifically noted at trial, this warning in no way reflected the performance of BELBCUA in its clinical trials and does not refute the enormous benefits in terms of safety and adverse events. (Tr.909:18-21.) For all the above reasons, the sales of BELBUCA have continued to rise in a market where sales of other opioids have fallen. (Tr.922:5-9, 922:20-25.)

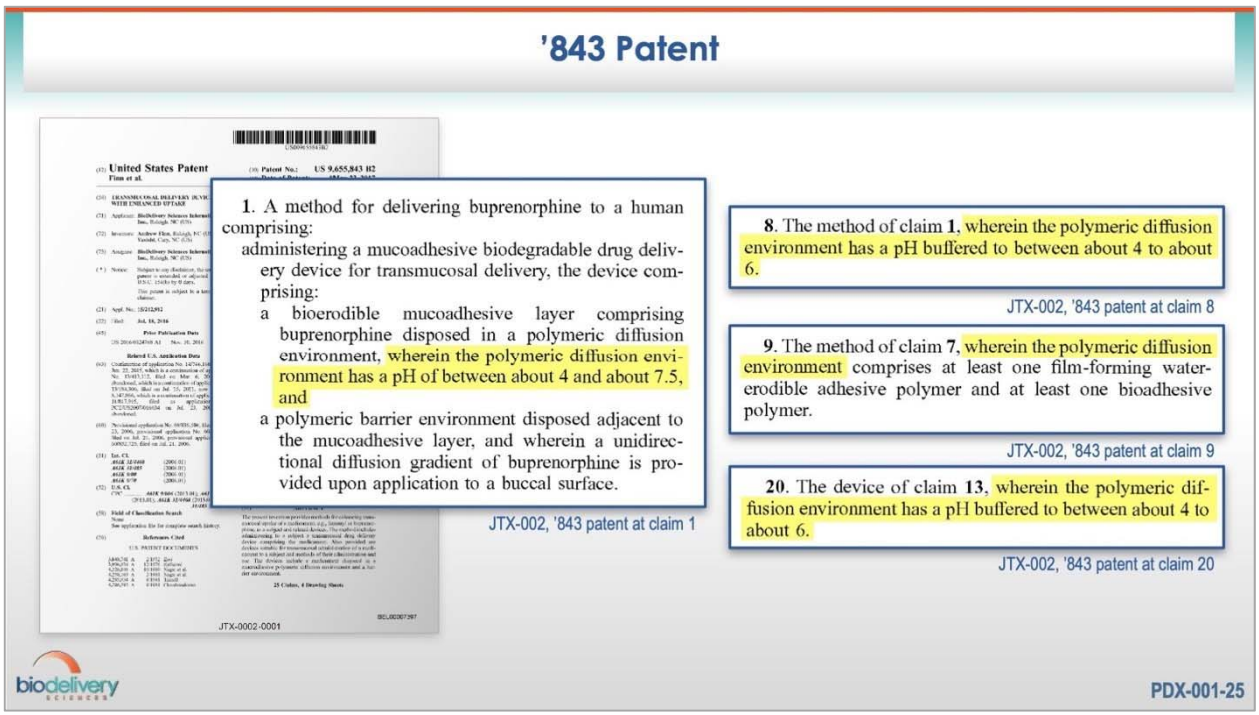
D. The Inventors Patented Their Claimed Devices and Methods of Obtaining Enhanced Uptake and Treating Pain

The ’866 patent claims methods of enhancing the uptake of buprenorphine using a two-layer device, which contains both a backing layer and a mucoadhesive layer containing a polymeric diffusion environment. (JTX-001, col.4:31-45, 6:25-32.) The polymeric diffusion environment is buffered to a pH of either about 4 to about 6 (claims 4 and 5) or between about 4.5 and about 5 (claims 3 and 10). The method provides for the rapid and efficient delivery of buprenorphine. The ’866 patent also claims devices containing the same features (claim 10). In addition, claim 4 of the ’866 patent recites achieving a first quantifiable plasma concentration of buprenorphine at about 45 minutes. Claim 5 of the ’866 patent recites achieving an effective plasma level for at least 4 hours. (JTX-0001-0019.)

Defendants admit that they infringe claims 3, 4, 5, and 10 of the '866 patent. (JTX-0001-0019.)



The '843 patent is a continuation of the '866 patent and shares substantially the same specification. (Tr.583:23-584:9.) Defendants admit that they infringe claims 8, 9, and 20. (JTX-002-0021.)



During prosecution of the ’866 patent, the Examiner agreed with the well understood characterization of the prior art discussed above, correctly explaining: “Buprenorphine is a weakly basic drug. Prior art Stanley et al. (U.S. Patent No. 5288497) teaches that administration of drugs through mucosal tissues generally occurs best when the drug is in the unionized form. Therefore, based on the teachings of Stanley et al. one of ordinary skill in the art would not have been motivated to utilize a low pH buffering system as most of buprenorphine is going to be in the ionized form and not the unionized form.” (JTX-0004-0341.)

Similarly, during prosecution of the ’843 patent, the Examiner confirmed the patentability of the asserted claims, stating: “As argued in the response filed as well as the declaration, the solubility of Guo and Todd is directed to the solubility

of buprenorphine in an aqueous environment wherein the instant claims have a unidirectional diffusion into the mucosal/buccal surface. Since the mucoadhesive layer of the instant claims and Moro is not an aqueous solution, the solubility of buprenorphine polymeric mucoadhesive layer cannot be extrapolated." (JTX-0005-2784.) Not only was Todd and Moro cited during the prosecution of the '843 patent, but the Examiner had another generic's (Teva's) invalidity contentions as well. (JTX-0005-2687-2692.) Teva was the first ANDA filer for BELBUCA. Teva's contentions argued that the '866 patent was obvious in view of Todd in combination with a Tapolsky reference and Todd in combination with Moro. (*Id*.) Todd and Moro are the same references Defendants rely on here.

Defendants attempt to discount the inventions of the '866 and '843 patents, alleging that the patents are merely an effort at "evergreening," i.e., that the patents are merely slight modifications of the prior art to extend the life of a marketed product. This allegation has no application here. The '866 and '843 patents are the first patents claiming a marketed dual-layer buprenorphine device with enhanced uptake and expire on July 23, 2027. BELBUCA was first marketed in early 2016 and was almost immediately challenged by Teva in a series of lawsuits first filed in 2016. These lawsuits were settled and allowed Teva to launch a generic version of BELBUCA in 2027, which was 6 months before the expiration of the '866 patent, which was the last patent-in-suit in that case. Defendants'

contention that Plaintiffs are somehow gaining more patent life than they are entitled to is wrong, particularly given the more than a decade it took to develop and bring BELBUCA to market.

III. THE ASSERTED CLAIMS OF THE '866 AND '843 PATENTS ARE NOT OBVIOUS

As detailed herein, the subject matter claimed in the '866 and '843 patents represent the epitome of a nonobvious invention.

A. Defendants Cannot Meet Their High Burden of Proof

As a patent is presumed valid under 35 U.S.C. § 282, a challenger must prove invalidity by clear and convincing evidence. *Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. 91, 100 (2011); *Glaxo Group Ltd. v. Apotex, Inc.*, 376 F.3d 1339, 1348 (Fed. Cir. 2004). Further, "[w]hen the prior art was before the examiner during prosecution of the application, there is a particularly heavy burden in establishing invalidity." *Impax Labs., Inc. v. Aventis Pharms. Inc.*, 468 F.3d 1366, 1378 (Fed. Cir. 2006) (citation omitted).

Obviousness is a question of law, which depends on underlying factual inquiries. *Endo Pharms Inc. v. Actavis,* LLC, 922 F.3d 1365, 1372 (Fed. Cir. 2019). Courts consider the so-called *Graham* factors, which include (1) the scope and content of the prior art, (2) differences between the prior art and the claimed subject matter as a whole, (3) the level of skill in the art, and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966); *KSR*

Int'l Co. v. Teleflex Inc., 550 U.S. 398, 406 (2007). To meet its burden of establishing obviousness, a defendant must show that one skilled in the art would have been motivated to take the necessary steps to arrive at the claimed invention with a "reasonable expectation of success." *Endo,* 922 F.3d at 1373; *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1069 (Fed. Cir. 2012); *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1356-57 (Fed. Cir. 2013); *Otsuka Pharm. Co., Ltd. v. Sandoz, Inc.*, 678 F.3d 1280, 1291-92, 1295 (Fed. Cir. 2012). Further, an invention is *not* "obvious to try," if it is more than a ''predictable use of known prior art elements.'' *Cyclobenzaprine*, 676 F.3d at 1073 (quoting *KSR*, 550 U.S. at 417); *Leo,* 726 F.3d at 1357.

The prior art as a whole must be examined as of the date of invention. *Otsuka*, 678 at 1295 ("Taken as a whole, however, the prior art taught away from using OPC–4392 as a starting point for further antipsychotic research.") All teachings must be considered, "including that which might lead away from the claimed invention." *In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988); *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011) (holding same). In carrying out this analysis, courts must be aware "of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning." *KSR*, 550 U.S. at 421; *Cyclobenzaprine*, 676 F.3d at 1079(recognizing "the danger of hindsight bias"). In

particular, "[t]he inventor's own path itself never leads to a conclusion of obviousness; that is hindsight." *Otsuka*, 678 F.3d at 1296.

B. Defendants Fail to Establish that a POSA Would Have Been Motivated to Combine the pH Ranges of the Liquid Formulation of Todd with the Solid Film Devices Described in Moro or Tapolsky-2005

Defendants fail to establish the requisite motivation to combine references by clear and convincing evidence.

1. There was no motivation to use buprenorphine in the devices of Tapolsky-2005 or Moro

Only through hindsight are Defendants able to argue that there was motivation to adapt buprenorphine into the devices of either Moro (DTX-178) or Tapolsky-2005 (DTX-173). Defendants fail to present any evidence that there were opioid formulations on the market using either the devices of Moro or Tapolsky-2005 as of the filing date of the '866 patent. It was the inventors of the '866 and '843 patents that first conceived the idea of using buprenorphine in a two-layered film device and brought it to market.

The Tapolsky-2005 reference relied on by Defendants is application 11/069,089, which was published on July 7, 2005. (DTX-173.) Initially, while Defendants refer to the '866 patent as using a "Tapolsky device," this is not accurate. Tapolsky-2005 does not describe a polymeric diffusion environment, as that term is understood in the context of the patents-in-suit. The '866 patent, for

example, describes that the "novel polymeric diffusion environment" enhances the "absolute bioavailability of the medicament contained therein," and provides "rapid onset." (JTX-0001, col.4:32-37; Tr.584:20-585:1.) The flux of the medicament from the polymeric diffusion environment into the mucosa can be enhanced by taking into the account the pH and the ionic nature of the polymers. (JTX-0001, col.6:16-24.) Here, as discussed above, it was the inventors of the patents-in-suit that developed the polymeric diffusion environment buffered to a particular pH range that resulted in "tremendous" and "unexpected" bioavailability for buprenorphine. (Tr.750:16-21,802:22-24.)

Tapolsky-2005 does not even discuss working with buprenorphine, much less discover a way to enhance its uptake. While Tapolsky-2005 mentions hundreds of different compounds that could be used, buprenorphine is *not* one of them. (DTX-173-0007-08; Tr.261:4-262:3.) In *Impax Labs., Inc. v. Lannett Holdings Inc.,* 893 F.3d 1372, 1379-80 (Fed. Cir. 2018), the court rejected a finding of obviousness where the prior art contained a "laundry list" of chemical compounds and the chemical later claimed in the patented invention was "mentioned once, with no further mention in an example or claim." Here, Tapolsky-2005 fails to even mention buprenorphine in its laundry list.

The closest Defendants can point to is butorphanol, but this compound is not mentioned in the section of the patent discussing "analgesics," but in an "other

pharmaceutical section." (DTX-173-0008, ¶53.) And Defendants' expert Dr. Fine did not even mention butorphanol as a commonly used opioid. (Tr.491:20-492:10.) The mere mention of butorphanol in a long laundry list of compounds would not lead a POSA to consider buprenorphine. This is particularly true given the structural differences between the two compounds and butorphanol's complex pharmacology. (Tr.744:22-745:20, 278:20-22, 256:13-15.) In fact, the evidence at trial established that all opioids do not work the same way in solid film devices. (*See* Tr.260:5-261:3, 754:24-756:7 (explaining how fentanyl and buprenorphine behaved differently with respect to pH and uptake in the patented device)).

Defendants now incorrectly allege, for the first time, that Plaintiffs' prosecuting attorneys made false statements to the PTO regarding "Tapolsky." (DBr.33,51.) During prosecution of the '866 patent, Plaintiffs' identified "Tapolsky et al. US Patent No. 6,159,498" as a prior art reference closely related to the pending claims. (JTX-004-0027.) In discussing that specific reference, Plaintiffs stated that "Tapolsky et al. does not teach administration of an opioid, including buprenorphine, or an opioid antagonist." (JTX-004-0033.) Contrary to Defendants' assertions, this statement is and was completely accurate as the '498 patent does not mention opioids or butorphanol. In contrast, Tapolsky-2005 (DTX-173), relied on here by Defendants is a different document and a subsequent application, which cites butorphanol in a laundry list.

Defendants also rely on a Moro reference. (DTX-178.) While Moro does list buprenorphine, it only does so among a "laundry list" of other chemical compounds and categories of chemical compounds, including antihistamines, vasoconstrictors, chemotherapeutic, hemostatic, antibiotic, keratolytic, hormone, and antiviral agents. (*See e.g.*, DTX-178, ¶¶17-24). This is insufficient to establish obviousness. *See Impax*, 893 F.3d at 1379-80. And none of the examples of Moro incorporate an active ingredient, much less buprenorphine. (Tr.263:5-7).

Each of the asserted claims of the '866 patent and the '843 patent require a buffered polymeric diffusion environment with a pH of either between about 4 to about 6 (claims 4-5 of the '866 patent and claims 8 and 20 of the '843 patent), or between about 4.5 and about 5 (claims 3 and 10 of the '866 patent).[2] Neither Moro nor Tapolsky-2005 has a polymeric diffusion environment buffered to *any* particular pH, much less the claimed pH values. (Tr.262:4-9, 652:3-5.)

2. There was no motivation to use the pH ranges in Todd's liquid formulation to achieve enhanced uptake in a solid film device

For the pH elements of the claims, Defendants rely on *at least* the Todd reference. (DTX-174.) Plaintiffs use the phrase "at least" because Defendants

[2] Claim 9 of the '843 patent requires a buffered pH of between about 4 and about 7.5.

apparently rely on a difficult to discern combination of up to 9 references. (DBr.16-27.)

Regarding Todd, the layered solid devices of Moro and Tapolsky-2005 containing polymers in the mucoadhesive layer are fundamentally different delivery vehicles than the sublingual liquid formulation of Todd. (Tr.652:8-654:14; DTX-174-0003.) Further, the pH range used in Todd was *not* for enhanced uptake and instead concerned the completely different problem of solubility. (Tr.653:4-654:2.) As Todd sought to make sublingual *liquid* formulations designed to stay under the tongue for some time, it was essential that the buprenorphine stay in solution. (Tr.652:21-653:9.) But given that it was a liquid, Todd had significant difficulties keeping the buprenorphine stable and not crash out of solution. (Tr.652:24-652:9; 265:21-266:2.) The author explained: "[w]e have found it very difficult to prepare stable aqueous solutions of adequate concentration for sublingual administration." (DTX-174-0003.) Thus, Todd used lower pH values for its formulation (in a range from 4.5 to 5.5) to increase the solubility of buprenorphine *and* also used 20 to 30 percent aqueous ethanol as a co-solvent to dissolve the buprenorphine and keep it in solution, as "[b]oth are required." (Tr.653:10-16.) Indeed, Todd states that it obtained higher uptake using *higher* pH values (pH of 5 and 6) but had to use the *lower* values to solve the solubility/stability issues he encountered with the liquid formulation. (Tr.671:16-

672:2, 733:7-734:13.) Todd is perfectly consistent with all the prior art discussed above, which taught that *increasing* the pH of a weakly basic compound—like buprenorphine—would increase absorption. (*See* §II.B., *supra*.)

Defendants argue that Todd obtained "good" bioavailability. (DBr.25.) But this statement is almost certainly made in comparison to oral bioavailability, which was only 10% due to the first-pass effect. (DTX-165-0004.) As shown in Johnson, aqueous solutions, using ethanol, like those in Todd, were only able to achieve bioavailability in the range of 30%. (DTX-165-0006.) And most importantly, the present invention is directed to enhanced bioavailability, not merely "good" bioavailability. The present invention's bioavailability far exceeds those of liquid solutions like Todd.

Further, Defendants present no evidence that the same solubility concerns present in the liquid solutions of Todd (or Cassidy) were present in a solid film device containing polymers, such as that in Moro or Tapolsky-2005—it is a completely different system. (Tr.653:22-654:18.) This was amply shown by the polymeric diffusion environment constructed by the inventors, which has a radically different solubility curve for buprenorphine than Cassidy, which generally applied to liquid formulations like Todd. (*Id*.) This is why the inventors initially tested formulations at pH's of 7.25 and 6.0, which were solubilized in the formulations they designed. (*See* §II.B., *supra*.) The inventors thought, as was

their experience with fentanyl, and consistent with all the prior art, that such higher pHs were more likely to lead to enhanced uptake. (*Id.*) That the lower pHs provided enhanced uptake was an unexpected surprise. (*Id.*)[3]

3. Defendants mischaracterize the prior art and the claimed invention.

Acknowledging the problems set forth above with merely relying on the combination of Tapolsky/Moro and Todd, Defendants seek to expand the prior art upon which they rely. But, in so doing, Defendants mischaracterize the teaching of the references to a POSA as of 2006.

Defendants argue that all the prior art discussed above did not apply to buprenorphine because, according to the Defendants, buprenorphine was *known* to behave differently than other weakly basic compounds, such as fentanyl. According to Defendants, the general laws of science that weakly basic compounds were absorbed better at higher pH values did not apply to buprenorphine. That is, using hindsight about how buprenorphine behaved in the claimed invention, Defendants argue that such behavior was known about buprenorphine in the prior art.

[3] Moreover, a POSA would have been reluctant to put buprenorphine at a low pH because of the risk of buprenorphine undergoing decomposition reactions. (Tr.745:21-747:19.)

However, Defendants' theory is inconsistent with all the prior art. *No* prior art reference dated before 2006 states that buprenorphine was expected to behave differently than all other weakly basic compounds. In fact, the prior art showed POSAs that buprenorphine, like all other weakly basic compounds such as fentanyl were expected to behave the same. For example, Cassidy explains the chemical properties of fentanyl and buprenorphine are very similar, stating that buprenorphine's "behavior in solution was similar to that reported for fentanyl and sufentanil, which are also weakly basic narcotic analgesics." (JTX-248-0008.) Similarly, Todd states that absorption of buprenorphine specifically was better at the *higher* pH values. (DTX-174-0003.)

Likewise, Weinberg explains that buprenorphine and fentanyl behaved very similar in the tested sublingual solutions. Weinberg hypothesized that "a low degree of ionization and a high lipid-to-water partition coefficient would favor maximal absorption. A class of weak bases (i.e., high pKas), the opioids at physiologic pHs, can exist in two forms; ionized or unionized. The *unionized* form is *favored* by a basic microenvironment." (JTX-249-0006.) Weinberg then explains how the data supported this hypothesis: "[m]ethadone, fentanyl, and buprenorphine, all of which have partition coefficients in excess of six times that of morphine, were absorbed to a very high degree. The more lipid-soluble drugs (Fig. 1)—buprenorphine, fentanyl, methadone, and heroin-were absorbed to the

greatest degree . . . ." (*Id.*) Weinberg further explains how the bioavailability results for buprenorphine and fentanyl tested at a pH of 6.5 in its sublingual system were basically the same. (*Id.*) And consistent with the hypothesis, Weinberg sought to test buprenorphine and fentanyl at even higher pH values but was limited due to the problems of "solubilizing" these drug in their sublingual liquid formulations. (*Id.*) Weinberg concludes by stating:

> A variety of opioid analgesics was tested for sublingual absorption. Increased lipid solubility and pH favoring unionization maximized concentration-independent drug absorption. Methadone, fentanyl, and buprenorphine were absorbed to the greatest extent . . .

(*Id.*, 0007.) There is nothing in Cassidy, Todd, or Weinberg that suggests that buprenorphine would achieve enhanced bioavailability to patients at lower pHs.

In 2007, in her role as an academic, Defendants' expert D. Michniak-Kohn wrote in her peer-reviewed book that "studies conducted with sublingual administration of opioids such as buprenorphine, methadone, and fentanyl showed increased absorption with increase in pH, where the drug was predominantly present in the unionized form (18.)" (DTX-355-0011.) The citation to "18 referred to by Dr, Michniak-Kohn is Weinberg. (DTX-355-0026.) This is how Weinberg was viewed as of the 2006 priority date of the patents-in-suit by Dr. Michniak-Kohn. Dr. Michniak-Kohn clearly did not think that buprenorphine behaved differently than other weakly basic compounds back in 2007.

Given the clear meaning of the prior art, Defendants' argument is based upon a revisionist re-interpretation of the references by Dr. Michniak-Kohn who now—some 14 years after her 2007 publication—claims the opposite should have been obvious to a POSA, even though it was not obvious to Dr. Michniak-Kohn. Dr. Michniak-Kohn apparently relies on the inventors' own work and her flawed understanding and application of the ionization states of buprenorphine as calculated by one of Plaintiffs' experts (Dr. Davies) using computer software in February 2020, all of which occurred well *after* the priority date of the '866 and '843 patents. (Tr.162:14-164:4.) While Dr. Michniak-Kohn states that she "believes" that Dr. Davies' data could have been calculated in the prior art (Tr.163:21-164:2), the issue is *not* what could have been done but what was actually done. And there is no evidence that anyone calculated the ionization states of buprenorphine using the "Henderson-Hasselbalch" formula as of 2006. (*Id*.)

Nevertheless, based on the ionization data for buprenorphine set forth by Dr. Davies, Dr. Michniak-Kohn, looking back at the prior art, argues that one would understand that at a pH of 6.5., buprenorphine was "nearly" a hundred percent ionized, thus Weinberg actually teaches the *opposite* of what the text states—that buprenorphine is absorbed better at *lower* pH's with more ionization.

Dr. Michniak-Kohn is wrong now in 2021. While she purports to rely on Dr. Davies' analysis, she misstates his opinions. Dr. Davies explained that if a

POSA had calculated the ionization states of buprenorphine in the prior art, a POSA would have learned that the non-ionized (unionized) form of buprenorphine "appears in a significant amount between about 6 and 12."" (Tr.730:13-15,734:9-10.) Thus, Dr. Davies testified that "a POSA would expect the most efficient uptake to be . . . between about 6 and 10." (Tr.741:12-18.)

The pH of 6.5 used in Weinberg is between 6 and 12 and is in the range Dr. Davies identified as having non-ionized buprenorphine molecules present in significant amounts. According to Dr. Davies' calculations, at pH 6.0, approximately 0.40% of buprenorphine molecules are unionized, and at pH 6.5, roughly 1.5% of buprenorphine molecules are unionized, meaning that the amount of unionized buprenorphine *more than triples* from pH 6.0 to pH 6.5. (DTX-377-0004.) Further, Dr. Davies confirmed that a POSA would have known that the *non-ionized form* of buprenorphine, with a higher pH, would absorb better through the mucosa due to the fatty-like nature of the membrane. (Tr.730:19-731:10.) This was also testified to by Dr. Taft and in the prior art discussed above. (*See* §II.B., *supra*.) This is also why Dr. Davies testified a POSA would have sought to use a pH values *higher* than 6.0 to obtain maximum absorption. (Tr.734:9-13.)

At most, Dr. Michniak-Kohn's analysis suggests that ionized buprenorphine is "soluble" and would be expected to cross the mucosa, such that it is bioavailable and can be "absorbed." (Tr.168:19-23; 170:5-9; 172:16-22; 175:16-25.) But this

is the wrong question. The question is not merely whether buprenorphine can be "absorbed." The point of the inventions claimed in the '866 and '843 patents is to *enhance* uptake and *increase* bioavailability. This is shown by the title of the patents, the abstract, the specification, and the language in the claims. (*See e.g.*, JTX-001-0001, 0006, 0007, 0018, claim 1; Tr.584:20-24.) And Dr. Michniak-Kohn *admits* that she did not even consider this question. (Tr.289:11-14.) This is also the reason why Plaintiffs argued at trial that Defendants' "two binary questions" (DBr.2) are insufficient to resolve the obviousness issues on certain claims. (Tr.144:25-145:18.) Defendants' questions ignore the salient issue of whether a POSA would have been motivated to use the claimed pH ranges with any reasonable chance of obtaining the enhanced uptake and bioavailability based upon the relevant prior art.

And the data relied on by Dr. Michniak-Kohn *confirms* that a POSA understood that to obtain enhanced uptake and improved bioavailability, such a person would have thought to use *higher*, not *lower* pH ranges. In terms of direct transmucosal delivery (through the buccal or sublingual oral mucosa), Dr. Michniak-Kohn relies on three references—Suboxone®, Todd, and Weinberg.[4] As

[4] Dr. Michniak-Kohn also relies on Birch, but this is a nasal formulation that is not relevant to either the claims of either the '866 or '843 patent, which are limited to the oral mucosa (the '866 patent), or the specific buccal mucosa (the '843 patent). D.I. 114 at 4; JTX0002-0021.

discussed below, the pH of Suboxone® was not known in the prior art. (*See* §III.F.2.c, *infra*.) Nevertheless, even if one considers that the Suboxone tablet has a pH of 3.5 (as argued by Defendants), that the Todd sublingual solution (containing 20-30% ethanol) has a pH of between 4.5 and 5.5, and the sublingual solution of Weinberg has a pH of 6.5, the following chart shows that for the prior art, as pH *increases*, bioavailability also increases whereas in sharp contrast, for the claimed invention, as pH *decreases*, bioavailability dramatically increases:

Prior Art	**pH**	**Bioavailability Improves with higher pH**		**BDSI Device[5]**	**pH**	**Bioavailability Improves with lower pH**
Weinberg[6]	6.5	55%[7]		BEMA 1	7.25	30.8%
Todd[8]	4.5-5.5	30%[9]		BEMA 3	5.4	46.1%
Suboxone®[10]	3.5	25%[11], 24.6%[12]		BEMA 7	4.75	**80.6%**

As shown above, Weinberg with a pH of 6.5 is more than *double* the bioavailability of Suboxone, which has an alleged pH of 3.5. Thus, the very

[5] All data from BEMA devices are described in JTX-365-0004.

[6] JTX-249.

[7] JTX-249-0006.

[8] DTX-174

[9] DTX-165-0006.

[10] JTX-365.

[11] DTX-165-0007, Fig. 3.

[12] JTX-365-0004.

references and data relied on by Dr. Michniak-Kohn show that a POSA would have believed that *increasing* the pH would *increase* bioavailability. This is what was also testified to by Dr. Williams, Dr. Taft, and Dr. Davies, and also the inventors of the '866 and '843 patents, who initially tested both their fentanyl and buprenorphine formulations at higher pH values. (*See* §II.B., *supra*.) No POSA would draw the conclusion from the left-hand chart above that a lowering the pH should be used to obtain enhanced uptake. Yet, this is precisely what the inventors found, as also as shown by the chart above. BEMA 7, with a pH of 4.75, has more than *double* the bioavailability of BEMA 1, with a pH of 7.25.

And this increase in bioavailability is not trivial. BEMA 7, for example, has some 228% bioavailability higher than Suboxone. As such, this case is directly analogous to *Orexo*, 903 F.3d at 1274, where the Federal Circuit found a 66% increase of bioavailability constituted strong evidence establishing the non-obviousness of the patented invention. The bioavailability obtained by the inventors here are even better and likewise establish non-obviousness.

This is also why Defendants' reliance on *Reckitt Benckiser Pharms. Inc. v. Watson Labs., Inc.*, C.A. No. 13-1674-RGA, 2016 WL 31876659, at *10 (D. Del. June 3, 2016) is misplaced. There, the issue was *not* enhanced bioavailability, as it is here, but whether a sublingual buprenorphine film, that attempted to *copy* the pharmacokinetic properties of Suboxone®, could be "absorbed" through the

mucosa at a low pH. *Reckitt*, 2016 WL 3186659 at *9-10. This Court found that notwithstanding the partition theory, buprenorphine could be absorbed through the mucosa at acidic pH values. *Id*. at *10. But that is *not* the issue here. The inventors were *not* trying to copy Suboxone, but rather to create a drug delivery device with enhanced bioavailability that had greatly improved pharmacokinetics over Suboxone—and they *succeeded* as reflected by the data above.

Additionally, the priority date of the patent in *Reckitt* was 2009, some three years after the priority date here, and the case involved different prior art. *Id*. at *2. Also, the film in *Reckitt* was manifestly different from the invention claimed here, as it did not have a backing layer and was designed to dissolve in the saliva of the mouth. *Id*. at *2-3. The claim at issue in *Reckitt*—unlike any claim here—recited a "local pH" range "in the presence of saliva" as the active agent dissolves in the mouth. *Id*. at *2,7. As stated by Plaintiffs' expert Dr. Williams, the issue in this case is *not* the local pH in saliva, but the pH of the polymeric diffusion environment. (Tr.611:20-612:22.)

The buprenorphine in the polymeric diffusion environment, as explained by Dr. Williams and Dr. Vasisht, is *already* dissolved in the polymers and exists as "dissolved molecules" as part of a molecular dispersion, also referred to as a solid solution. (Tr.588:12-20, 751:10-752:10, 756:8-757:1.) There are no solid "particles" of buprenorphine that first need to dissolve in saliva or become

"hydrated." (*Id.*; Tr.752:4-10.) This allows buprenorphine to diffuse "directly into the mucosal layer." (Tr.586:21-587:19, 593:8-13.)

Dr. Michniak-Kohn testified incorrectly that for the device to work, it must first dissolve in saliva. (Tr.611:20-612:22.) Dr. Michniak-Kohn, who did no testing of her own (Tr.257:21-24), has never designed or developed any transmucosal products, or even worked with marketed opioids (Tr.295:6-23), simply does not understand the invention, and certainly not better than Dr. Vasisht, the inventor, who successfully designed and marketed fentanyl and buprenorphine transmucosal products (Tr.755:1-12), or Dr. Williams who also successfully designed buccal products for the delivery of opioids (Tr.582:3-582:15).

Finally, the references and arguments relied on by Defendants, particularly the combination of Moro and Todd, were before the Examiner during prosecution. (*See* §II.D., *supra*.) This makes it even more difficult for Defendants to carry their burden of proof. *Impax Labs.*, 468 F.3d at 1378. Defendants have failed to meet their burden of showing the requisite motivation by clear and convincing evidence.

C. There was No Reasonable Expectation of Success of Obtaining Enhanced Uptake Using the pH Range Described in Todd

Even if there was motivation to prepare a buprenorphine formulation using the pH ranges of Todd, which there was not, a POSA would not have reasonably expected the huge gains in bioavailability and C_{max} achieved by the claimed invention. (*See* §III.B., *supra*.) The bioavailability obtained by BEMA 7 is

80.6%, as high as that obtained from intramuscular injection. (Tr.524:4-18, 802:13-24.) Neither Todd nor any other prior art reference discloses anything that would lead a POSA to expect the dramatically improved Cmax and bioavailability discovered by the inventors.

For claim 9 of the '843 patent, the pH range is between about 4 and about 7.5. Dr. Michniak-Kohn admitted that the prior art was *unable* to formulate buprenorphine at pH's higher than 6.5, stating that one could not even dissolve the buprenorphine. (Tr.169:19-170:2, 170:20-22, 176:1-9.) Yet, the inventors created formulations at a pH of 7.25 that worked better than Suboxone®. (JTX-001, Fig. 4.) Dr. Michniak-Kohn's own testimony establishes that there was no expectation of success in obtaining the full range for claim 9 of the '843 patent.

D. Defendants cannot show there was Motivation to Meet the Pharmacokinetic Elements of Claims 4 and 5 with a Reasonable Expectation of Success

Claims 4 and 5 of the '866 patent have additional pharmacokinetic elements. Claim 4 of the '866 patent requires that "a first quantifiable plasma concentration of buprenorphine is observed at about 45 minutes," and claim 5 requires that "an effective plasma concentration of buprenorphine is maintained for at least 4 hours." (JTX-001-0019.) Thus, even if Defendants were to show that the pH ranges in claims 4 and 5 are obvious, they would still need to show that these

additional elements are obvious to render claims 4 or 5 invalid. *Shelcore, Inc. v. Durham Indus., Inc.*, 745 F.2d 621, 624 (Fed. Cir. 1984). And this they cannot do.

Defendants incorrectly allege that Tapolsky-2005 teaches the plasma concentration element of claim 4. (DBr.38-39.) Tapolsky-2005, however, does not describe working with buprenorphine. (Tr.421:17-19.) Nor does Tapolsky-2005 disclose any pharmacokinetic measurements in humans (D.I. 249, 2), let alone any plasma concentrations of buprenorphine in humans (Tr.262:13-15). Rather, the parts of Tapolsky-2005 relied on by Defendants (Example 40 and Table 5) describe "systemic plasma levels obtained at different intervals" for discs loaded with "0.9 mg albuterol sulfate" in dogs. (DTX-173-0015; Tr.422:19-22.) A POSA, however, would not have believed that the pharmacokinetics of transmucosal absorption of albuterol sulfate in dogs is applicable to the transmucosal absorption of buprenorphine in humans. (Tr.808:16-809:6, 742:9-19, 423:3-5, 743:23-744:9.) The physical and chemical nature of albuterol sulfate is also very different from that of buprenorphine. (Tr.423:3-11, 256:13-15, 743:2-743:5, 744:10-15.)

Further, even if such data was applicable to buprenorphine, Defendants are incorrect that Tapolsky-2005 describes a mean plasma albuterol sulfate concentration at 45 minutes as required by claim 4. Tapolsky-2005 reports plasma levels of albuterol sulfate concentration at time interval 0. (Tr.809:7-809:25.)

Contrary to Defendants' assertions, Tapolsky-2005 does not state that this measurement is "background" noise. (Tr.809:19-25.) Tapolsky also fails to disclose what constitutes an effective plasma concentration of albuterol sulfate. (Tr.422:24-423:2; 810:9-20.)

Defendants next argue that the first quantifiable plasma concentration is somehow "inherent" in Tapolsky-2005. This argument was not raised by Defendants before or during trial and is thus waived. But even if considered, inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Endo Pharm. Sols., Inc. v. Custopharm Inc.*, 894 F.3d 1374, 1381 (Fed. Cir. 2018). "[T]hat which may be inherent is not necessarily known" and that which is unknown cannot be obvious." *Honeywell International Inc. v. Mexichem Amanco Holding*, 865 F.3d 1348, 1354 (2017). As noted above, Tapolsky-2005 does not describe working with buprenorphine, and its examples describe working with different chemical compounds in dogs. A POSA would have understood that different drugs have different rates of absorption, and plasma concentration levels depend on the drug, the device, the dose, and the subject. (Tr.256:13-15, 325:16-19, 813:4-7.) Tapolskly-2005 does not inevitably result in the pharmacokinetic properties for buprenorphine recited in claims 4 and 5.

Defendants rely on Bullingham-I in an attempt to fill in these missing elements. Bullingham-I, however, is directed to sublingual tablets for the treatment of acute post-surgical pain along with the concomitant use of intravenous buprenorphine. Bullingham-I assessed patients who were undergoing hip surgery, during which, patients were given an intravenous dose of buprenorphine over a three-hour period (from 0 to 180 minutes), and blood samples were collected. (Tr.811:14-812:11.) At the three-hour point, the patients still had a considerable amount of intravenous buprenorphine in the bloodstream. (*Id*.) Following surgery, patients were administered two tablets sublingually, each containing .2 mg buprenorphine for a total of .4 mg buprenorphine and additional blood samples were collected for up to 180 minutes. (*Id*.)

The authors purported to provide certain pharmacokinetic data for the buprenorphine sublingual tablets. But because of the presence of the intravenous buprenorphine, the results were compromised. Dr. Taft, a recognized expert on pharmacokinetics, testified: "If you look at the plasma levels of buprenorphine from the intravenous dose at the time the sublingual tablets were introduced, that's the primary contributor to the plasma levels that were measured in the patient. That between 0 and 45 minutes after the tablets were introduced, the intravenous in dose is what's driving the effect." (Tr.818:2-9.)

In an attempt to address the impact of the intravenous dose of buprenorphine, Bullingham I attempted to "strip" out the intravenous plasma data from the sublingual data. (Tr.332:23-334:9, 812:12-24; DTX-077-0002.) But this so-called stripping technique was scientifically flawed because the authors used a yardstick—the "mean terminal exponential decay rate"—from a different study with *different* patients. (Tr.812:12-814:17, 408:10-19; DTX-077-002.) As testified by Dr. Taft, this introduced significant "variability and errors" into the study. (Tr.813:23-814:4.) For this reason, within the first hour where the intravenous contribution is most prevalent, a POSA would understand that pharmacokinetic data for sublingual tablets was not reliable. (Tr.814:5-17, 817:18-820:3.)

This is further shown by the data set forth in Table 2, which has a value of .10 ng/ml at 40 minutes, plus or minus .12, which is the standard error of the mean. (DTX-077-0003; Tr.815:23-816:1.) This suggests that "within one standard error the value is 0. It's not detectable." (*Id*.) Dr. Taft explained that "it's clear to me at the 40-minute time point, that is not a quantifiable concentration, and I don't believe a person of ordinary skill would think it was either." (Tr.816:16-25.) Likewise, Defendants' expert Dr. Shafer testified that Bullingham-I does not provide buprenorphine plasma concentrations at 45 minutes. (Tr.403:11-13.)

Defendants have not established the requisite clear and convincing evidence to establish the obviousness of claim 4.

Similarly, due to the confounding comingling of the intravenous and sublingual administration, Bullingham-I also does not establish the obviousness of claim 5, which requires an effective plasma concentration for buprenorphine that is maintained for at least four hours. (JTX-0001-0019.) As Dr. Taft explained, and as shown by the reference itself, Bullingham-I does not even include the plasma concentration of buprenorphine after 3 hours because the *last* measurement was taken at 180 minutes (3 hours). (Tr.820:12-821:4; DTX-077-0002.) Thus, the study could not possibly teach or report an effective plasma concentration for at least 4 hours as in claim 5. (*Id*.)

Defendants argue that Bullingham-I shows that the patients experienced analgesia for over 4 hours, some "534 minutes" (DTX-077-0003.) But, again, a POSA would not believe that such analgesia was solely due to the sublingual tablets given the concomitant use of intravenous buprenorphine. Furthermore, in addition to the intravenous buprenorphine, after 6 hours, the patients could press a button in which a "pump" provided 2.5 milligrams of a different medicine, diamorphine. If the button was pressed five times, it was determined that the patient needed more pain medication. (Tr.821:5-822:14; DTX-077-0002.) Not only was the standard of "five presses" arbitrary, but there was also no questioning

of the patient of how much pain they were in – the appropriate method for evaluating pain levels in patients. (*Id.*; *see also* Tr.389:11-390:12.) A POSA would not understand that "analgesia" data from intravenous buprenorphine, sublingual tablets, and a third pain medication taught an effective plasma concentration exclusively from the sublingual tables for four hours or that such data could even be extrapolated from the sublingual tablets to the entirely different two-layer buccal film. (Tr.820:4-822:14.)

The above points are reinforced by Bullingham-II (DTX-177), which was a similar study to Bullingham-I, but there, the same authors extended the plasma sampling time from three to ten hours. (Tr.823:3-6.) Table 6 of Bullingham-II shows that for the sublingual tablets, the first measurable plasma occurred at 60 minutes, *not* 45 minutes as required by claim 4. (DTX-177-0007; Tr.823:11-824:6, 825:2-11.) Before this time, Table 6 reports that the plasma concentration due to the sublingual tablets is zero. (*Id.*) Bullingham-II further shows that Defendants have failed to show that claim 4 is obvious.

Bullingham-II also demonstrates that the "at least four hours" element of claim 5 is not met by Bullingham-I. Bullingham-II states that a minimally effective plasma concentration is between 0.4 and 0.6 ng/ml. (DTX-177-0005; Tr.825:15-23.) For the .4 mg sublingual tablet, which is the strength of the tablet described in Bullingham-I, Table 6 shows a plasma concentration first reaching .4

ng/ml at 180 minutes, but such concentration *only* lasts until 210 minutes, and then falls below .4. at 240 minutes. (Tr.826:20-827:15.) Thus, Table 6 reports an effective plasma concentration lasting well below the four hours required by claim 5. (*Id.*; 416:8-417:21.)

Finally, Defendants incorrectly argue that the pharmacokinetic parameters in claims 4 and 5 of the '866 patent are "not meaningful." (DBr.40.) The parameters, however, are important as they are commonly used to assess how the medicine will behave in humans and whether it will have favorable pharmacokinetics. This is why such numbers were recorded by the inventors in the underlying study (BUP-101) (JTX-352-0017) and described in the patent (JTX-001, col.26, Table 4). Further, to the extent the numbers are "not meaningful," this would be immaterial. Courts do not consider "policy considerations" in interpreting claims or in applying the precedent of the Federal Circuit. *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1339-40 (Fed. Cir. 2005). Further, it is Defendants' burden to establish invalidity of each claim, not Plaintiffs' burden to argue patentability. *Shelcore, Inc. v. Durham Indus., Inc.*, 745 F.2d 621, 624 (Fed. Cir. 1984). Claims 4 and 5 were found patentable by the PTO and are not obvious in view of the prior art.

E. The Objective Indicia Further Demonstrates the Non-obviousness of the Patents-In-Suit

Evidence concerning the objective indicia of non-obviousness, such as long-felt need, unexpected results, and teaching away, must be considered before the court reaches an obviousness determination as a means to guard against the impermissible use of hindsight. *See Apple Inc. v. Samsung Elects. Co., Ltd.*, 839 F.3d 1034, 1052 (Fed. Cir. 2016); *Plantronics, Inc. v. Aliph, Inc.*, 724 F.3d 1343, 1354-55 (Fed. Cir. 2013); *In re Cyclobenzaprine*, 676 F.3d at 1075-80. Such evidence prevents courts from using hindsight to reconstruct the invention from the prior art by "develop[ing] a hunch that the claimed invention was obvious, and then con-struct[ing] a selective version of the facts that confirms that hunch." *In re Cyclobenzaprine*, 676 F.3d at 1079 (citation omitted).

1. The Prior Art Taught Away from the Claimed Invention

One such objective indicium is whether the prior art teaches away from the claimed invention. *See Tec Air, Inc. v. Denso Mfg. Michigan Inc*, 192 F.3d 1353, 1359-60 (Fed. Cir. 1999). Here, the prior art specifically taught that *increasing* the pH was likely to lead to enhanced uptake. (*See* §II.B., *supra*.) The inventors surprisingly and unexpectedly found the exact opposite was true in the claimed invention. (*Id.*)

2. The Claimed Subject Matter Satisfied a Long-Felt Need

Long-felt but unmet need is also important evidence. *See Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 662-63 (Fed. Cir. 2000). It is reasonable to infer that the need would not have persisted had the solution been obvious. *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1332 (Fed. Cir. 2016). A new formulation of a known drug that effectively treats patients with reduced side effects can satisfy a long-felt need. *See Forest Labs, LLC v. Sigmapharm Labs LLC*, 918 F.3d 928, 936-37 (Fed. Cir. 2019). To assess the presence of a long-felt need, the Court looks to the filing date of the invention. *Proctor & Gamble v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 998 (Fed. Cir. 2009). Further, the amount of time that passed between the prior art teaching the components and the eventual successful creation of the invention "speaks volumes to the non-obvioussness of the [patents-in-suit]." *Leo*, 726 F.3d at 1359.

Plaintiffs' expert Dr. Rauck, a leading physician in the area of pain treatment and a lead clinician for the clinical trials for BELBUCA, testified regarding the long-felt need for a product like BELBUCA.[13] As of the 2006 filing date of the '866 and '843 patents, there was a need for an alternative treatment to marketed opioids that could treat chronic pain patients with lower risk of abuse and death and that had fewer side effects. (Tr.859:17-863:23, 874:14-23; JTX-403.) By this

[13] Even the FDA itself turns to Dr. Rauck when it has questions in the area of pain treatments, including how to design clinical trials. (Tr.862:21-863:17; JTX-466.)

time, deaths attributed to the use of opioids, such as fentanyl, hydromorphone, morphine, oxycodone, and oxymorphone, were rapidly increasing in the United States. (*See* §II.A, *supra.*) Further, opioids also caused significant side effects in patients that were a major impediment to treatment, including severe constipation. (*See id.*) The inventions claimed in the '866 and '843 patents satisfied this long-felt need. BELBUCA, which is an embodiment of the asserted claims,[14] met the long-felt need for an effective chronic pain treatment with lesser incidences of adverse events, including the potentially lethal effect of respiratory depression and severe constipation. (*See* §II.C., *supra.*)[15]

Defendants incorrectly argue that long-felt need can be ignored because there is no nexus between the claimed devices and the properties of BELBUCA. There is, however, "a presumption of nexus for objective considerations when the patentee shows that the asserted objective evidence is tied to a specific product and that product is the invention disclosed and claimed in the patent." *Immunex Corporation v. Sandoz Inc.*, 964 F.3d 1049, 1067 (Fed. Cir. 2020); *WBIP*, 829 F.3d at 1329 (holding same). Here, the long-felt need evidence is tied to BELBUCA,

[14] D.I. 245.

[15] The need is not to resolve the entire opioid crisis as Defendants imply, but rather to create a safer form of chronic pain treatment for patients with a lower risk of abuse and adverse events. BELBUCA® solves that need.

and Defendants have admitted that BELBUCA is covered by the claims of the patent. That is all that is required

Defendants suggest that all the properties of BELBUCA need to be claimed to rely on them as objective indicia. There is no authority for Defendants' position, and *Immunex* stands for the contrary position. The clinical efficacy of Enbrel and its commercial success at issue in *Immunex* were not cited in the patent claims.[16] Similarly, in *Sigmapharm,* the Federal Circuit found a long-felt need where the claim recited a sublingual tablet that disintegrated in a certain amount of time but the long-felt need evidence pertained to its reduced side effects as compared to other antipsychotics. *Sigmapharm*, 918 F.3d at 932, 936. The Federal Circuit, in *Genetics*, also explained how properties of the claimed subject matter need not be known at the time of patenting and do not need to be claimed to constitute objective indicia. 655 F.3d at 1307. In contrast, Defendants rely on *Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1373 (Fed. Cir. 2019). But *Fox* refers to a bicycle chain and discusses where "the patented invention is only a component of a commercially successful machine or process." *Id*. That is not the situation here.

[16] *See Immunex Corp. v. Sandoz Inc.*, 395 F.Supp.3d 366, 376-80 (D.N.J. Aug. 9, 2019).

3. The Enhanced Bioavailability and Plasma Concentrations Achieved by the Claimed Invention Constitute Strong Evidence of Unexpected Results

Unexpected results are also an important indicator of non-obviousness. *See United States v. Adams*, 383 U.S. 39, 51-52 (1966); *Leo,* 726 F.3d at 1358. Here, the enhanced uptake, as measured both by C_{max} and bioavailability, remains a surprising and unexpected result of the claimed invention. (Tr.759:13-760:11, 771:21-772:6, 650:9-21, 799:21-804:1.) A POSA would not have expected the trend in the data, that as the pH decreases, the bioavailability and C_{max} increases. (*Id*.) This is the opposite of what the prior art suggested. (Tr.802:25-803:18.)

The unexpected results of the claimed invention are further supported by *Orexo,* 903 F.3d at 1274. There, the Federal Circuit held that a "66% improvement in bioavailability" over Suboxone was more than a mere difference "in degree," and found the patent at issue non-obvious. The results achieved by the claimed invention are far better and were achieved by the inventors some six years before the 2012 filing date of the patent at issue in *Orexo*.

Suboxone, which was the only orally-administered buprenorphine product on the market in 2006, had a bioavailability of about 25%. (JTX-365-0004; Tr.521:12-24.) The methods/devices of the claimed invention have bioavailability values ranging from 32% to 80.6% or from 20% to 228% higher bioavailability than Suboxone. If one just considers the pH ranges recited in claims 5 and 10 of

the '866 patent, the bioavailability values range from 165% to 228% higher. Plaintiffs' expert Dr. Taft testified that the 80.6% value (for BEMA 7) value is "tremendous for a non-IV formulation. That's exceptional. And so these are unexpected results based on the pH partition theory." (Tr.802:22-24.)

Further, these results have practical consequences. Enhanced uptake means less buprenorphine is required, which results in an improved side effect profile and little to no respiratory depression. (*See* §II.C., *supra*.) Defendants incorrectly assert that respiratory depression is irrelevant because it is not recited in the claims. As set forth in *Genetics*, unexpected results need not be claimed, included in the specification, or even known as of the filing of the patents in suit. 655 F.3d at 1307. This is because, as explained by the Federal Circuit, "[r]elevant secondary considerations often are not manifest even until well after the issuance of a patent." *Id*. Defendants assertions to the contrary are wrong.

F. Defendants' Attempt to Shift the Burden of Proof Should be Rejected

As Defendants have no credible response to this strong evidence of non-obviousness, Defendants resort to a series of baseless attacks on the inventors, asserting that they intentionally made "material" misstatements to the PTO. Such serious allegations should be considered allegations of inequitable conduct and subject to the Federal Circuit's high bar for both intent and materiality. But because Defendants did not raise inequitable conduct as a defense (as they could

never meet the requisite high bar),[17] Defendants instead cite case law from different circuits in the 1960's and 1970's—*before* the formation of the Federal Circuit—cases which used different standards for assessing when and how allegedly false statements affect the presumption of validity. (DBr.51-52.) None of these arguments, however, were raised in Defendants' pleadings, their contentions, their expert reports, or the Pre-trial Order, which can only be modified for "to prevent manifest injustice." (Del. L. R. 16.3(d)(4).) All of these arguments are thus waived. Nevertheless, even if considered, Defendants' assertions are wrong both as a matter of law and fact.

1. Defendants' burden-shifting argument is wrong as a matter of law

The cases relied on by Defendants are not even remotely good law. The Federal Circuit was created in 1982 for the purpose of harmonizing patent law between Circuits and eliminating the different standards for validity defenses, including inequitable conduct, that led to rampant forum shopping. S. Rep. No. 275, 97th Cong., 2d Sess. at 5-6 (1982), reprinted in 1982 U.S.C.C.A.N. 11, 15-16; H.R. Rep. No. 312, at 20-23, at 22, 22 97th Cong., 1st Sess. 20-23 (1981); Robert J. Goldman, Evolution of the Inequitable Conduct Defense In Patent Litigation, 7 HARV. J. LAW & TECH. 37, pg. 67 (1993).

[17] In fact, when asked if inequitable conduct or "something like that" was an issue in the case, Defendants did not say that it was. (Tr.187:24-188:18.)

And the Federal Circuit has made clear that with regard to patent issues, or even issues implicating patent issues, its precedent controls—not those of the regional circuits. *Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc.*, 75 F.3d 1568, 1574 (Fed. Cir. 1996) (explaining that "a question concerning whether alleged inequitable conduct in the prosecution of a patent application constitutes unfair competition clearly does impact our exclusive jurisdiction. We therefore do not defer to regional circuit law on this issue."); *see also Chrysler Motors Corp. v. Auto Body Panels of Ohio, Inc.*, 908 F.2d 951, 953 (Fed. Cir. 1990). Thus, Defendants' reliance on pre-1982 regional circuit cases as supporting burden shifting in patent cases due to alleged misstatements to the PTO contradicts binding Federal Circuit precedent.

The Federal Circuit has explained that "[a]bsent proof of inequitable conduct, the examiner's or the applicant's absolute compliance with the internal rules of patent examination becomes irrelevant after the patent has issued." *Magnivision. Inc. v. Bonnaeu Co.*, 115 F.3d 956, 960-61 (Fed. Cir. 1997) (stating that it is "simply incorrect" that "the presumption of validity could be lost by . . . 'prosecution irregularities.'"). The Federal Circuit realized that spurious allegations about inventors' conduct had become "an absolute plague" on the patent system, where lawyers advanced the most serious of allegations on the "slenderest grounds." *Therasense, Inc. v. Becton, Dickinson & Co.*, 649 F.3d

1276, 1289 (Fed. Cir. 2011) (en banc). To avoid making such allegations routine, the Federal Circuit required that to establish an intent to deceive sufficient to affect the presumption of validity, Defendants must establish by "clear and convincing evidence" that "the specific intent to deceive must be 'the single most reasonable inference able to be drawn from the evidence.'" *Id*. at 1290. "Hence, when there are multiple reasonable inferences that may be drawn, intent to deceive cannot be found." *Id*. at 1290-91.

And "the materiality required to establish inequitable conduct is but-for materiality. When an applicant fails to disclose prior art to the PTO, that prior art is but-for material if the PTO would not have allowed a claim had it been aware of the undisclosed prior art." *Id.* at 1291. The one exception is "egregious conduct" due to the submission of "an unmistakably false affidavit." *Id*. at 1292. Defendants have not come close to satisfying this standard, or that of intent, which has never been raised in this case and was never pled.

As Defendants cannot show inequitable conduct the presumption of validity remains—as always—on the Defendants. *See Microsoft*, 564 U.S. at 108–12 ("Nothing in § 282's text suggests that Congress meant . . . to enact a standard of proof that would rise and fall with the facts of each case.") Defendants' arguments should be seen for exactly what they are—a desperate effort to salvage their failure to meet their high burden of proof.

2. Defendants' arguments are wrong as a matter of fact

a. Statistics

Defendants argue that the data set forth in the Finn declaration can be ignored because the declaration does not show statistics, which allegedly should have been provided to the PTO. (DBr.36.) But there was no requirement to provide the PTO with a statistical analysis. (Tr.941:9-942:7.) In any event, Dr. Thisted (a world-renowned biostatistician), reviewed the underlying data[18] and calculated the relevant statistics and determined that all the devices with a pH range of between about 4 and about 6 have C_{max} values that are statistically significantly greater than Suboxone® (Tr.943:14-944:2), which is the closest prior art and thus correct comparison for purposes of unexpected results. *See Millennium Pharmaceuticals, Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1368 (Fed. Cir. 2017). Defendants presented no contrary statistical modeling at trial.

Further, Dr. Thisted explained that statistics are not necessary to see the novelty of the invention given the clear trend in the data of increasing bioavailability with decreasing pH. (Tr.941:9-942:7.) There was also a clear difference in C_{max} between BEMA 1 and 2, and that the highly statistically significant differences between BEMA 3-7 compared to BEMA 1 give a POSA confidence that the differences between BEMA 2 and BEMA 1 are not due to

[18] *See* JTX-352-007; JTX-353-2009, 1123, 2004; JTX-0349-0042-43.

chance or random variation. (Tr.944:3-945:19.) Finally, Dr. Vasisht testified that statistics were not necessary to demonstrate the differences between BEMA 1 and 2 for formulation screening. (Tr.758:12-19.)

b. Defendants have not proven that Suboxone® has a "buffered" environment

Defendants argue that Dr. Finn falsely stated that Suboxone® was "unbuffered." (DBr.4,33-34.) The term "buffered" means a "stabilized pH," not merely a measurable pH at any given time (JTX-001,col.12:36-37.)

Having challenged Dr. Finn, it is Defendants' burden to prove that Suboxone was buffered. However, the only document cited by Defendants on this issue (DTX-0172) actually supports the accuracy of Dr Finn's statement. Consistent with Dr Finn's statement, DTX-0172 does not say that Suboxone is buffered. Indeed, Defendants had several years to conduct discovery from third parties. If they truly believed Suboxone was buffered, they could have tried to prove it. Tellingly, they never sought any discovery from the Suboxone manufacturer.

Instead, Defendants note that that Suboxone may have used citric acid and sodium citrate at some undefined date. From this, Defendants speculate that that Suboxone is "buffered" because these two chemicals can be used as buffers. But there is nothing in DTX-0172 that states that Suboxone is actually "buffered" with a stabilized pH or that that these chemicals have been used as buffers for the purpose of stabilizing pH. Dr. Williams, one of the foremost experts in

formulation science, testified that there are uses for sodium citrate and citric acid other than as buffers, and that it is incorrect to speculate that Suboxone is buffered simply because of the alleged use of these ingredients. (Tr.694:18-20; 699:9-14.)

And whether Suboxone® was or was not buffered would have had no impact on the unexpected bioavailability data set forth in the chart. (Tr.702:21-703:8.) The whole point of paragraphs 8-9 of the Finn declaration were to explain how reducing the pH unexpectedly and surprisingly enhanced the bioavailability of buprenorphine in the buccal film device he invented. Dr. Finn then compared Suboxone to the other BEMA devices. The data showed that the BEMA devices that were buffered to a pH of about 4 to 6 had remarkably enhanced bioavailability, including as compared to Suboxone.

Finally, the document DTX-172 that Defendants cite as the Suboxone "label" is actually a communication between the makers of Suboxone® and the FDA. Defendants have not provided any evidentiary foundation to show that this FDA communication with the makers of Suboxone was publicly available as of the date of the Finn declaration, nor did Defendants establish where this document even came from or that Dr. Finn had ever even seen it. *See Blue Calypso, LLC v. Groupon, Inc.*, 815 F.3d 1331, 1348-49 (Fed. Cir. 2016) (holding that publication from internet was not prior art because challenger failed to prove that it was "disseminated to the interested public before the critical date.")

c. The pH of Suboxone

Defendants also allege that Dr. Finn was untruthful because Suboxone has a pH of 3.5, but Dr. Finn did not include this in his declaration, which states the pH of Suboxone was "N/A".[19] Dr. Finn's declaration was dated in 2011 and the study comparing BEMA devices 1 and 2 with Suboxone were performed in 2006. (JTX-352-0002.) Dr. Michniak Kohn testified that the pH of Suboxone was not known in the art, and Defendants cannot point to anything in the scientific literature as of 2006 or 2011 that states the pH of the Suboxone tablets. (Tr.154:11-155:18.) Instead, Defendants rely on a declaration ("Reitman") that that was made 2014 in an IPR for a different patent where a Dr. Reitman measured the pH of Suboxone as 3.5. (DTX-365.)[20] Dr. Finn could not have known about testing that occurred in 2014 when he filed his declaration in 2011.

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[19] Defendants never questioned Dr. Finn about this because this was never an issue in the case.

[20] Tellingly, Defendants never relied on Reitman until right before trial, when they raised this in a new reply report by Dr. Michniak-Kohn. Plaintiffs moved to strike the new opinions and evidence in this report as untimely, but it was denied by the Magistrate Judge. (Oral-Order, Feb. 17, 2021.) Respectfully, Reitman should not have been admitted into evidence. A statement by a party's expert is not an admission of a party under Fed. R. Evid. 801(d)(2)(C) or (D). *Pernix Ir. Pain DAC v. Alvogen Malta Operations Ltd.*, 316 F. Supp. 3d 816, 820, 823 (D. Del. 2018)(citing *Kirk v. Raymark Industries, Inc.*, 61 F.3d 147 (3d Cir. 1995)). Nor is Reitman an adopted statement, admissible under Rule 801(d)(2)(B). *Id*. at 824. In *Pernix*, this Court did not find that an expert statement was adopted even though the party designated the experts, served expert reports, made them available for

Defendants, however, argue that the pH of Suboxone is an inherent property of the tablet and is thus part of the prior art. But inherency "may not be established by probabilities or possibilities." *Endo*, 894 F.3d at 1381. The only evidentiary foundation that the pH of 3.5 was inherent was the testimony by Dr. Michniak-Kohn that Dr. Reitman test in 2014 was "simple" and could have been performed in the prior art. (Tr.161:13-14.) While perhaps "simple," Defendants did not provide any evidence that a POSA would have used this test with this amount of water in the prior art. Dr. Williams offered unrebutted testimony that there was no standard technique for dissolving a tablet in water to determine its pH in either the prior art or even today and that the amount of water used in the test would affect the results. (Tr.703:9-704:6.) Defendants have also not put in any evidence to show that the formulation for Suboxone in 2014 was the same formulation as in 2006. Thus, Defendants have failed to satisfy their burden of showing that a Suboxone® tablet would necessarily have a pH of 3.5.

Defendants assert that Plaintiffs argued that the pH of Suboxone "can be readily obtained in a matter of minutes by anyone with deionized water and a pH meter." (DBr.27.) Defendants, however, *admit* this quote comes from an

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deposition, and identified them as trial witnesses. *Id*. at 825. The same analysis applies to Reitman.

unverified document, which was not admitted into evidence. (DFF¶95, n.3.) Plaintiffs had no opportunity to question any witness about this document, and the document and assertions Defendants say it supports should be stricken from Defendants' brief and findings. Further, that one can dissolve a Suboxone® tablet in ionized water misses the point. The relevant issue is that the amount of water used will impact the pH, and Dr. Williams gave unrebutted testimony that there was no standard procedure in 2006 for how much water to use.

Finally, had Dr. Finn actually known that the pH of Suboxone was 3.5, this would have made his declaration even stronger because, as discussed above, Suboxone's bioavailability is quite poor at only 25%—as would have been expected based on the prior art. Defendants' allegation that Dr. Finn was untruthful by omitting pH information about Suboxone not known in the prior art—a fact conceded by Defendants' own expert—is absurd.

d. pH values for BEMA 1 and 2

Defendants argue that BDSI told the FDA that the pH values for BEMA 1 and 2 are not 7.25 and 6.0, but instead are 6.8 and 5.3. (DBr.35-36.) Defendants, however, rely on part of the NDA submitted by Endo Pharmaceuticals to the FDA in 2014, *not* statements made by or on behalf of BSDI. There is no explanation or foundation for when or how Endo came up with its numbers, whether they were obtained by Endo under similar conditions, whether Endo was reporting the same

or different testing, or even whether Endo reported this information correctly to the FDA in 2014. (Tr.290:13-20.)

Moreover, BUP-101 was a study conducted in 2006 by an independent third party contractor ("CEDRA") for BDSI. (JTX-352-0002.) The study was conducted to FDA standards. (JTX-365-0003, ¶8.) BUP-101 reported that the pH values for BEMA 1 and BEMA 2 were 7.25 and 6.0, just as set forth in the declaration. (*See e.g.*, JTX-352-0011, 0013, 0014, 0015, 0022, 0024, 0027.) Dr. Finn testified that the pH values for BEMA 1 and 2 in his declaration came from the BUP-101 study. (Tr.772:7-14.) There is no evidence in the record that CEDRA contrived the results from BUP-101 study or that there is anything wrong with the data. And BDSI's own version of the pharmaceutical development report, which was also signed, reviewed, and approved by Endo personnel, describes the pH of the first two formulations as 7.25 and 6. (DTX 0019-0027, 0003.) There is no evidence in the record that Dr. Finn made any false statements.

Further, even assuming the pH values for BEMA 1 and 2 were 6.8 and 5.3, this would not have impacted the examination of the patents or the unexpected nature of the data in the chart. (Tr.851:15-20, 852:9-17.) A pH value of 6.8 is high, and a POSA, specifically in light of Weinberg, would have believed that this pH would have led to maximum absorption. That the lower pH's led to

"tremendous" bioavailability values remains unexpected. (Tr.802:13-24, 852:6-17.)

Finally, testing for BEMA devices 3, 4, 5, 6, or 7 (the accuracy of which has not been challenged), show increasing bioavailability as pH is lowered. (JTX-365-0004.) This data is also reported in the underlying clinical reports, which are admitted into evidence, and Defendants have not challenged such data. (*See* JTX-352-0011; JTX-353-2009, 1123, 2004; JTX-0349-0042-43.)

IV. THE ASSERTED CLAIMS OF THE '866 AND '843 PATENTS ARE NOT ANTICIPATED

The '915 application is a priority application for the '866 and '843 patents and was filed in July 2007. Defendants argue that the '866 patent cannot claim priority to the '915 application and is thus anticipated by its subsequent publication in July 2008. For patent claims to be entitled to the priority date of an earlier-filed application, the earlier-filed application must contain adequate written description support for those claims. *Hologic, Inc. v. Smith & Nephew, Inc.*, 884 F.3d 1357, 1361 (Fed. Cir. 2018). To satisfy the written description, there must be enough description to show that an inventor actually invented the subject matter later claimed. *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351, 1355, 1357 (Fed. Cir. 2010) (en banc).

Defendants contend that the asserted claims of the '866 patent and certain claims of the '843 patent are not entitled to the earlier filing date of the '915

application because the priority application does not provide sufficient description of the claimed pH range of about 4 to about 6 for the polymeric diffusion environment (’866 patent, claims 4-5; ’843 patent claims 8, 20) or about 4.5 to about 5 (’866 patent, claims 3,10).

This argument makes no sense. Dr. Michniak-Kohn testified that paragraph 60 of the Vasisht-I application describes these very pH ranges in support of her argument that Vasisht-I anticipates the claims of the ’866 patent. (*See* DFF ¶¶ 273-275.) Vasisht-I, however, is the *same* application as the ’915 application.[21] Dr. Michniak-Kohn’s contradictory arguments that the application dose *not* describe the pH ranges for priority but *does* describe the pH limitations for anticipation should be rejected.

Indeed, the ’915 application *does* describe the pH ranges claimed in the ’866 and ’843 patents stating that the pH of the mucoadhesive polymeric diffusion environment may be “between about 4.0 and about 7.5”, “about 6.0”, and “that all values and ranges between these values and ranges are meant to be encompassed

[21] Dr. Michniak-Kohn relied on paragraph 60 of Vasisht-I, which is PCT application PCT/US2007/0 16634, to argue anticipation. (DTX-017-0001-line 21,0018.) The ’915 application, however, is the *same* application, PCT/US2007/0 16634. (DTX-206-0001, line 86.) The only difference between DTX-017 and DTX-206 is that the numbering of the paragraphs is slightly different. For this reason, paragraph 60 of Vasisht-I is identical to paragraph 63 of the ’915 application.

by the present invention." (DTX-206, ¶63.) This language supports the claimed ranges. (Tr.656:1-23.)

Additionally, ¶63 states that "the pH of the device may be about 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, or 7.5, or any incremental value thereof." (DTX-206, ¶63.) These numbers provide even additional support. (Tr.656:24-657:5.) Defendants argue that because the "device" has two layers, this sentence refers to the device "as a whole" as opposed to the pH of the mucoadhesive layer. (DBr. 61-62.) But the question is not whether the claimed devices have two layers—they do— but whether a POSA would understand that the inventors were using the "pH of the device" as merely a shorthand for "the pH of the mucoadhesive layer of the device" in the context of this particular sentence. The answer is plainly "yes." (Tr.657:6-21,659:13-17.)

The '915 application *only* discloses adjusting and measuring the pH of the polymeric diffusion environment of the mucoadhesive layer. (Tr.657:11-21.) There is no discussion of measuring the pH of the device as a whole or the backing layer. (*Id.*) Indeed, the entirety of ¶63 refers to the pH of various "embodiments" of the mucoadhesive polymeric diffusion environment. (DTX 206, ¶63.) And the discussion is in a section of the patent discussing the polymeric diffusion environment, as shown by preceding and later paragraphs. (Tr 657:22-658:7; DTX 206, ¶¶ 62-67.) Moreover, Example 1 teaches making three batches of the

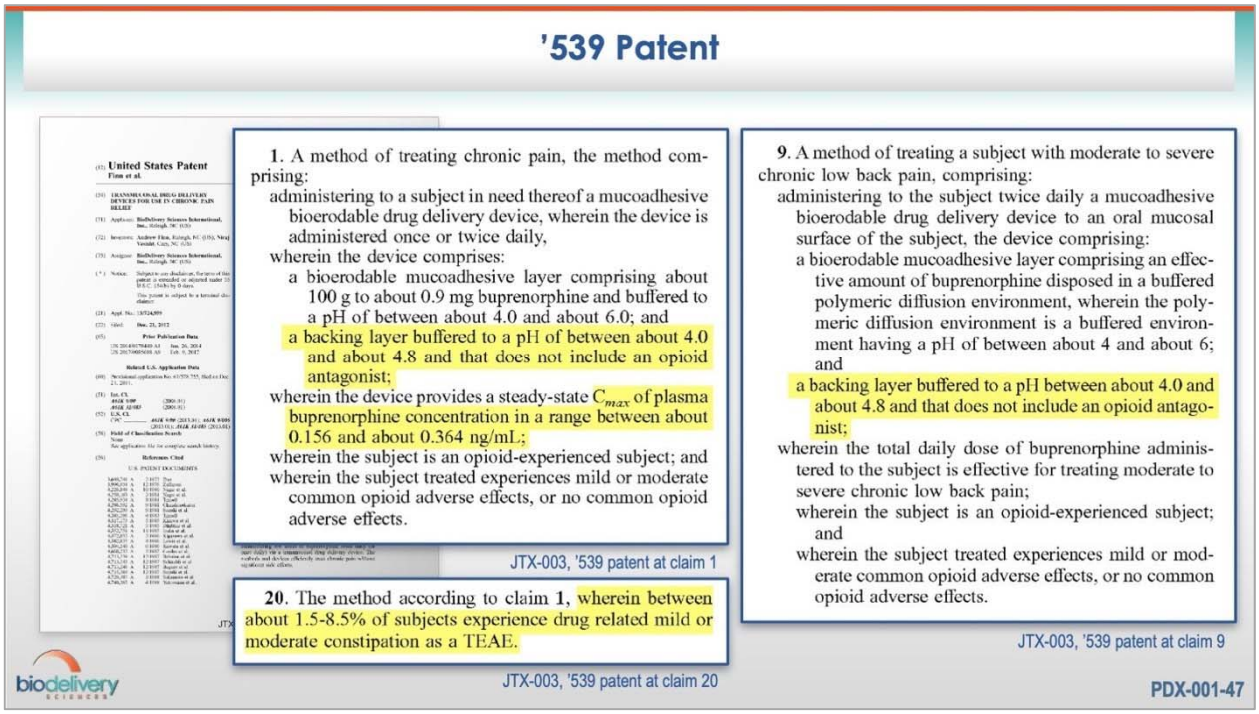
mucoadhesive layer and adjusting their pH values to 6, 7.25. and 8.5. (DTX-206, ¶103; Tr.658:8-24.) Devices with mucoadhesive layers having these pH values are later referred to in the patent as a "device at pH 6," "a device at pH 7.25," and "a device at pH 8.5." (Tr.658:25-659:17.) Unquestionably, these pH values are referring to the pH of the mucoadhesive layers, and the "device at pH 6" is a shorthand abbreviation. (Tr.659:13-17.) The sentence in ¶63 was using "pH of the device" in the very same way. (*See also* DTX-206, ¶124 citing to Example 1 and referring to "exemplary devices of the present invention (at pH 6 and 7.25)".) The '915 patent application supports the asserted claims.

The asserted claims of the '866 and '843 patents are also supported by the '726 application, which is an earlier application filed on July 21, 2006. (Tr.659:18-662:20; JTX-238.) The '726 application describes that "the device comprises buprenorphine disposed in a mucoadhesive layer comprising having a pH between about 4 and about 7.5." (JTX-238, Abstract, Tr.660:9-18.) All the pH ranges claimed by the '866 and '843 patents are within this range of pH values. The '726 application also states, as a shorthand abbreviation, that "the pH of the device may be about 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, or 7.5, or any incremental value thereof." (JTX-238, ¶20; Tr.660:9-18.) The abstract and the preceding paragraphs make clear that the application is only discussing measuring the pH of the mucoadhesive layer. (JTX-238-0024, ¶¶ 2, 18, 23; Tr.660:19-661:12.)

Further, the '726 application *only* teaches measuring the pH of the mucoadhesive layer and has an example that *only* adjusts and measures the pH of the mucoadhesive layer. (Tr.661:13-662:20; JTX-238, ¶62.) Accordingly, the asserted claims are entitled to the filing date of the '726 application as well. There can be no anticipation.

V. THE ASSERTED CLAIMS OF THE '539 PATENT ARE NOT ANTICIPATED OR OBVIOUS

The '539 patent was filed in 2012 and contains the results of a clinical trial with BELBUCA. (JTX-003-0012-0015.) The asserted claims of the '539 patent recite treating methods of chronic pain (claim 20) and treating chronic back pain (claim 9). (JTX-003-0016.)



Unlike the claims of the '866 and '843 patents, the claims of the '539 patent all recite a backing layer having a particular pH—between 4.0 and 4.8. (*Id.*) After the effective filing date of the '866 and '843 patents, and during the further development of BELBUCA, the inventors discovered that the pH of the backing layer was also impacting the absorption of buprenorphine across the mucosa. (DTX-0019-0033; PTX-608-0056; JTX-353-0026; PTX-0325-0029.) Nothing in the prior art teaching this unexpected property of the backing layer. (Tr.804:2-806:19.) In addition, claim 9 of the '539 requires that the subject receiving the device experience only moderate or mild side effects as was learned in the clinical trial. (JTX-0003-0016). Claim 20 requires this as well, but also requires that only between 1.5 to 8.5% of the subjects experience constipation, and that the device provides a specific C_{max} between 0.156 and about 0.364 ng/ml. (*Id.*)

A. Defendants have failed to Show that Claim 9 is Anticipated

Defendants argue that Claim 9 of the '539 patent is anticipated by Vasisht I. (DBr.43-46.) This argument, however, was not raised before trial and is thus waived. Defendants had only alleged that claim 9 was obvious. (*See* D.I. 229, Ex. 3A at 180.) Further, Defendants are wrong that Vasisht I anticipates claim 9.

"[I]n order to demonstrate anticipation, the proponent must show 'that the four corners of a single, prior art document describe every element of the claimed invention.'" *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir.

2008) (internal quotation omitted). Additionally, "the prior art reference—in order to anticipate under 35 U.S.C. § 102—must not only disclose all elements of the claim within the four corners of the document but must also disclose those elements 'arranged as in the claim.'" *Id.* Further, enablement and anticipation are separate questions: "Whether a prior art reference is enabled is a separate question from whether it discloses, expressly or inherently, the claimed limitations at issue." *Galderma Labs, L.P. v. Teva Pharms USA, Inc.*, 799 F. App'x. 838, 844 (Fed. Cir. 2020). Further, it is legal error for a court "to fill in missing limitations simply because a [POSA] would immediately envision them." *Id*. at 845.

Based on these legal principles, Defendants cannot prove anticipation by clear and convincing evidence. Claim 9 does *not* recite a method of "treating a subject for pain," but instead recites a more specific method of "treating a subject with moderate to severe chronic low back pain." (JTX-003-0016.) Although enabled, this precise limitation of the claim is not described in Vasisht-I. The only mention of back pain discussed in Vasisht-I is the following: "breakthrough pain also occurs in patients with lower back pain." (DTX-017, 0008-0009, ¶29.) Vasisht-I, however, distinguishes "breakthrough pain" from chronic pain" in that very paragraph. (*Id.*) Thus, Vasisht-I does not describe this claim element.

Similarly, claim 9 requires that the subject "experiences mild or moderate common opioid adverse effects, or no common opioid adverse effects." (JTX-

0003-0016.) Again, while this claim element is also enabled by Vasisht-I, the application does not describe this limitation such that there can be anticipation. The paragraph relied on by Defendants in DFF-175, DTX-0017, ¶118, describes the side effects for a *fentanyl* device being "mild or moderate." That a POSA could "envision" this level of side effects from Vasisht-I for buprenorphine, or that Vasisht-I enables a device containing buprenorphine that produces such side effects, is not sufficient for anticipation under *Galderma.*

Additionally, Vasisht-I does not describe the pH of the backing layer that is recited in claim 9. Defendants agree that the pH is not described (Tr.279:7-12) but argue that it is inherent. But rather than making the formulation described in Vasisht-I and testing it, which is the usual way to establish inherency, Defendants only provide conclusory and inaccurate testimony from their expert. *See Schumer v. Lab'y Computer Sys., Inc.,* 308 F.3d 1304, 1315-16 (Fed. Cir. 2002) ("[T]estimony is insufficient if it is merely conclusory").

Defendants state that BELBUCA has a backing layer with a pH between 4.0 and 4.8, which Plaintiffs agree. (Tr.576:13-25.) Defendants then argue (based on testimony from Dr. Michniak-Kohn) that the backing layer described in example I of Vasisht-I, which was the backing layer for a fentanyl device, is "materially identical" (DBr.44) to the formulation for BELBUCA and thus the pH in Vasisht-I "must necessarily be the same," i.e., about 4.5. (DBr.44-45.)

But as shown at trial, the formulations are *not* the same. The formulation in Vasisht-I is based on a wet formulation, while the formulation for BELBUCA is based on a dry formulation. (DTX-0017,¶99; DTX-0019-0045,n.1; Tr.206:23-207:5.) Dr. Michniak-Kohn stated that that the proper way to convert Vasisht-I to a dry formulation is to divide by .222. (Tr.281:9-12.) Dr. Michniak-Kohn, however, admitted that she rounded the resulting numbers to *one* decimal point. (Tr.283:8-15.) She also rounded the numbers of the backing layer for BELBUCA to one decimal point. (DBr.44.) This rounding was not innocuous, however, as it masked the differences between the different formulations, as seen by the following chart:

Component	Backing layer of Vasisht I, dry formulation % weight, ***not*** rounded to one decimal point	Backing layer of BELBUCA, dry formulation % weight, ***not*** rounded to one decimal point	Percent difference
Sodium benzoate	0.450	0.495	**10%**
Methylparaben	0.450	0.449	0.2%
Propylparaben	0.135	0.090	**50%**
Citric Acid	0.450	0.495	**10%**
Vitamin E Acetate	0.045	0.045	(no difference)
Saccharin Sodium	0.450	0.495	**10%**

Hydroxypropyl Cellulose	63.063	63.154	0.1%
Hydroxyethyl Cellulose	31.532	31.543	0.03%
Titanium Dioxide	2.703	2.471	**9%**
Peppermint Oil	0.901	0.764	**17.9%**

The numbers for "most" of these components are *not* "exactly in the same percent by weight," as testified by Dr. Michniak-Kohn. (Tr.207:6-11.) There are material differences in the bolded percentages set forth above, i.e., the amount of sodium benzoate (10%), propylparaben (50%), citric acid (10%), saccharin sodium (10%), and titanium dioxide (9%), peppermint oil (17.6%). Dr. Michniak Kohn agreed that peppermint oil and titanium dioxide were different (Tr.207:12-13), but she ignored the other differences—like the 50% for propylparaben (Tr.283:8-15)—due to her rounding error. Defendants' assertion that the backing layer of Vasisht-I inherently has the same pH as BELBUCA because it has the same formulation is not correct and falls well-short of clear and convincing evidence.

In fact, unlike Dr. Michniak-Kohn, who could have performed testing but chose not to (Tr.257:21-23), during prosecution Dr. Vasisht had a contract manufacturer remake the backing layer from example 1 of Vasisht-I. The average pH value was 5.61. (JTX-0006-4101, ¶7.) Rather than confirming the differences in the backing layers, Defendants again, without citing any testimony from Dr.

Vasisht, accuse Dr. Vasisht of either having "falsified or omitted material data." (DBr.46.) But this assertion is based solely on Dr. Michniak-Kohn's flawed opinions, and such accusations without any supporting evidence is baseless. Further, the allegation that Dr. Vasisht intentionally falsified data was not in the Pre-trial order or any contention in this case. Defendants' unsubstantiated, belatedly raised allegations against Dr. Vasisht should be rejected.

B. Defendants have Failed to Show that Claim 9 is Obvious

Defendants argue —in a footnote— that if the Court finds that the claim 9 is not anticipated, then it must be obvious. (DBr.45, n.21.) This falls well short of the necessary clear and convincing evidence of motivation and a reasonable expectation of success needed to find a claim invalid. *See Wasica Fin. GmbH v. Cont'l Auto. Sys., Inc.*, 853 F.3d 1272, 1286 (Fed. Cir. 2017) (affirming rejection of conclusory argument that invention would have been obvious if not anticipated.)

Further, given the difference in formulations of the backing layer set forth above, Defendants have not explained why a pH of between about 4.0 and 4.8 would have been obvious. Defendants also offer no explanation for why the backing layer's effect on uptake would have been reasonably expected by a POSA. Dr. Taft provided unrebutted evidence at trial, explaining how raising the pH of the backing layer unexpectedly decreased uptake across the buccal mucosa. (Tr.804:2-806:19.) It is legal error to dismiss "properties of the claimed invention as merely

inherent, without further consideration as to unpredictability and unexpectedness." *Honeywell*, 865 F.3d at 1354. "What is important regarding properties that may be inherent, but unknown, is whether they are unexpected." *Id.* at 1355. The unexpected properties of the backing layer refute Defendants' obviousness theory.

C. Claim 20 of the '539 Patent Would Not Have Been Obvious

Claim 20 requires a backing layer with a buffered pH between about 4.0 and 4.8. (JTX-003-0016.) Thus, for the reasons set forth above, this claim is also not obviousness in view of Vasisht-I.

Additionally, claim 20 requires that only 1.5 to 8.5% of the subjects experience mild to moderate constipation. (*Id.*) While Vasisht-I states that the devices described therein will cause "little to no constipation" it does not render obvious the specific percentages later claimed by the '539 patent. Defendants have not established the size of the genus of "little constipation" or explained how many species fall within the scope of the genus. *See Wasica*, 853 F.3d at 1286 (explaining that conclusory testimony without establishing the size of the genus and the number of species will not render a particular species obvious). Further, Defendants base their obviousness position on the conclusory testimony of Dr. Fine that "constipation is a side effect that results from the drug and dosage amount, not the drug delivery system." (DBr.48.) But the novel and unobvious devices of the '539 patent with enhanced uptake and improved bioavailability *do*

allow the usage of *less* of a dose of buprenorphine. In addition, the Temgesic label Defendants rely on refers *both* to sublingual tablets and buprenorphine given by intravenous injection, which by-passes the gastrointestinal tract and is why the rates of constipation are low. (DTX-0170-0001.)

Further, Defendants rely on Reder (DTX-078) in an attempt to show that the C_{max} limitation in claim 20 is obvious.[22] However, Reder teaches a completely different formulation, a transdermal patch that delivers buprenorphine over a long period of time. This is the opposite of the buccal-film-devices of the '539 patent designed for an immediate release that allows the medicant to get into the bloodstream quickly, which is a benefit in treating chronic pain. (Tr.829:23-830:19.) While Defendants rely on Reder's statement that buccal or sublingual delivery can be used, they ignore the language that such administration "may be utilized to attain the above plasma concentrations over time." (DTX-0078, col.3:56-57.) The "above plasma concentration over time" discuss a slow "72 hour dosing interval." (*Id*, col.3:24-25,34-35.) And in the very next sentence, Reder

[22] Defendants also rely on Bullingham-I and Bullingham-II for purported Cmax values of sublingual tablets but acknowledge that the disclosed Cmax data is outside the steady-state Cmax range recited in claim 20. (DBr. 50, n.24.) Moreover, a POSA would not have been motivated or reasonably expected to successfully achieve the claimed steady state Cmax range based on Bullingham-I and Bullingham-II due to the compromised data from the "stripping" methodology discussed above.

states that "it is preferred that the buprenorphine is administered via a transdermal delivery system or via continuous infusion." (*Id*., col.3:63-65.) This is because the transdermal delivery system and continuous infusion provide a flatter continuous profile of the plasma concentration to better control plasma concentrations of buprenorphine. (Tr.287:4-12,424:18-425:5,423:19-23,830:5-19.) All the examples of the patent teach either transdermal delivery or intravenous infusion. (DTX-0078-0019-0026.) Thus, Reder teaches away from the immediate delivery system claimed in the '539 patent, and described in Vasisht-I, and instead describes a slow-sustained-release formulation where either transdermal or intravenous delivery is preferred. (Tr.830:5-834:16.) A POSA would not be motivated to combine Reder with Vasisht-I, and Defendants have failed to show that claim 20 is obvious.

D. There was Long-felt Need for the Devices Claimed in the '539 Patent

The evidence of long-felt need described above also applies to the '539 patent, filed in 2012. Even by this date, the only other buprenorphine product available was Butrans®, which is a transdermal patch approved in 2010. (JTX-417.) While Butrans® was approved for chronic pain, it had many limitations. Most importantly, Butrans® was only approved in low doses (maximum of 20 micrograms per hour) that for many patients is a "limited dose and ineffective dose." (Tr.915:24-916:11, 551:25-552:17; JTX-0460-0002.) There was a concern

that Butrans® in doses above 40 micrograms caused an elevated risk of QT prolongation. (Tr.896:22-897:12.) Accordingly, Butrans® was only approved in the U.S. at lower doses and, as of the 2012 filing date of the '539 patent, carried a black box warning about QT risk. (*Id*; Tr.552:18-25, 554:18-23; JTX-0417-0001.) In contrast, at doses up to 900 micrograms, "there has not been any dose that has been linked to QC prolongation with BELBUCA." (Tr.911:7-13,912:7-23.) For BELBUCA, a maximum dose of 1800 micrograms can be administered (900 twice daily), but for Butrans®, the maximum dose is 450 micrograms or four times less. (Tr.915:24-916:11,911:7-13,912:7-23.) This is a significant benefit to patients in chronic pain who need to take the medicine for long periods of time. (*Id*.)

Further, because Butrans® is a patch, it had many other problems, including that the patch did not stay on the skin, that a patient had to rotate its placement, that irritation issues developed at the application site, and that the patch was impacted by humidity and sweat. (Tr.765:25-766:2,895:3-5.) Even after three weeks, the application sites remained extremely "red and irritated," and the patch thus has "real problems with patients with tolerability secondary to irritation at the site of application." (Tr.895:22-896:2.) Butrans® simply did not solve the long-felt need for a safe and effective medicine that could treat chronic pain as of the 2012 filing date of the '539 patent. Further, to the extent there is any controversy regarding

the date when a POSA became aware of the opioid crisis, there can be no doubt that it was well-known as of the filing of the '539 patent in 2012.

VI. CONCLUSION

Accordingly, the Court should find that Defendants have failed to prove by clear and convincing evidence that the asserted claims the '866, '843 and '539 patents are invalid.

MORRIS, NICHOLS, ARSHT & TUNNELL LLP

Dated: May 26, 2021

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The undersigned counsel hereby certifies that the foregoing document contains 17,470 words, which were counted by using the word count feature in Microsoft Word, in 14-point Times New Roman font. The word count includes only the body of the brief. The word count does not include the cover page, tables, or the counsel blocks.

Date: May 26, 2021

/s/ Jeremy A. Tigan

Jeremy A. Tigan (#5239)

CERTIFICATE OF SERVICE

I hereby certify that on May 26, 2021, I caused the foregoing to be electronically filed with the Clerk of the Court using CM/ECF, which will send notification of such filing to all registered participants.

I further certify that I caused copies of the foregoing document to be served on May 26, 2021, upon the following in the manner indicated:

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